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PROLONGED UNINTERRUPTED CORTISONE THERAPY IN RHEUMATOID ARTHRITIS

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A little more than two years have elapsed since Hench, Kendall, Slocumb, and Polley (1949) first reported that the adrenocortical hormone, cortisone, and pituitary adrenocorticotropic hormone (A.C.T.H.) exerted powerful antirheumatic effects when administered to patients with rheumatoid arthritis. This epochal discovery opened new avenues of approach to the many unanswered basic problems of the disease, and engendered hope that these endocrine substances might be directly applied for the practical benefit of patients. Unprecedented amounts of clinical and laboratory research have already been accomplished, and, as knowledge has accumulated, the usefulness and limitations of cortisone and A.C.T.H. as therapeutic agents have become clearer.

The application of cortisone as a practical treatment for rheumatoid arthritis is beset with problems. When the hormone is administered to patients with active disease the reversible manifestations improve with remarkable promptness and consistency, but unfortunately the benefits are not lasting and symptoms reappear with impressive regularity when it is withdrawn. The favourable action of cortisone is suppressive only, not curative, and its administration probably does not alter the eventual course of the disease. As rheumatoid arthritis is a chronic and often progressive malady, it follows, from the facts now available, that if improvement is to be sustained cortisone must be given more or less continuously for an indefinite period of time.

Patients with rheumatoid arthritis present no clinical signs of adrenocortical deficiency (Hench *et al.*, 1950a ; Sprague *et al.*, 1950b), and by gross and histological examinations their adrenal glands are not anatomically changed (Sokoloff *et al.*, 1951). Recent laboratory studies suggest, however, that the urinary excretion of steroids may be quantitatively altered and that either the production or metabolism of adrenal cortical hormones may be abnormal (Dobriner, 1951). Nevertheless, the amounts of cortisone required for desirable antirheumatic response appear to be substantially greater than the quantities of corticosteroids which are produced by the patient's own adrenal glands under normal circumstances. It is therefore logical to assume that the suppression of rheumatoid arthritis which results from cortisone administration is due to an exogenously induced state of hormone excess rather than to the correction of a glandular deficiency with substitution therapy (Sprague *et al.*, 1950a). But cortisone is a potent agent which is capable of exciting diverse physiological activities in many organs and tissues. When a state of hypercortisonism is continued, a variety of metabolic and hormonal manifestations may develop, many of which are objectionable from the standpoint of treatment.

Morphological changes of a regressive nature have been repeatedly observed in ductless glands following the administration of large amounts of hormone secreted by the gland. More relevantly, atrophy of the adrenal cortices has been demonstrated in experimental animals (Ingle, 1938 ; Ingle and Mason, 1938 ; Antopol, 1950 ; Winter *et al.*, 1950) and in humans (Sprague *et al.* 1950a) following the use of large amounts of cortisone. During treatment with the hormone certain laboratory tests, such as the eosinopenic response to A.C.T.H. and the urinary excretion of 17-ketosteroids, indicate that adrenocortical function is depressed (Forsham *et al.*, 1950b ; Sprague *et al.*, 1950a ; Dobriner, 1951). With short-term or relatively short-term administration, such functional arrest is temporary and the tests revert to normal after cortisone is withdrawn. Studies relating to functional recovery after long-term therapy have not yet been reported, however, and fear has been voiced that the prolonged use of cortisone might induce irreversible atrophy and permanent adrenal cortical insufficiency.

These considerations prompt three pertinent questions bearing on the practicability of employing cortisone continuously for long periods : (1) Can satisfactory suppression of rheumatoid arthritis be maintained indefinitely or will refractoriness to the drug and deterioration of improvement eventually occur ? (2) Will continued administration be accompanied by unfavourable hormonal effects of such numbers and intensity as to necessitate discontinuation of treatment ? (3) Will prolonged administration, especially if continuous, cause irreparable damage to vital organs such as the adrenal cortices ?

With these questions in mind, a study of the effects of prolonged uninterrupted cortisone acetate therapy in patients with rheumatoid arthritis was undertaken.* The results of this investigation constitute the basis for the present report.

*The cortisone acetate used, and hereinafter referred to as cortisone, was supplied in part through the courtesy of the Medical Department of Merck & Co., Inc., Rahway, N.J.

Selection of Patients and Plan of Investigation

A total of 76 patients with chronic rheumatoid arthritis were started on treatment between January 1 and August 31, 1950. It was planned to continue cortisone administration for prolonged periods in each instance, but treatment was discontinued in 16 patients within six months for various clinical reasons. The 60 remaining patients received the hormone without interruption for periods ranging from 6 to 15 months; the average duration of treatment for these was 10.2 months, and 27 patients were treated for more than one year.

Each of the 76 patients had active rheumatoid arthritis with reversible changes, but various degrees of disease severity, functional impairment, and structural change were embraced by the group. The arthritis was graded as severe in 36 patients, moderately severe in 27, moderate in 12, and mild in 1. Articular involvement was restricted to peripheral joints in 56 patients, to the spine in 3, and 17 had combined peripheral and spinal arthritis. Forty-five of the patients were women and 31 were men, and their ages ranged from 19 to 80 years.

During cortisone administration no other medications designed to influence the course of the disease or to provide symptomatic relief were permitted. Salicylates or other analgesics, physiotherapeutic measures, and other supportive adjuncts were stopped at the beginning of the treatment.

Route of Administration

Intramuscular administration was used exclusively during the early months of the investigation. Since June, 1950, when it was learned that cortisone was effective by mouth (Freyberg *et al.*, 1950), the majority of patients have received oral preparations; most of those initially treated by the intramuscular route were transferred to oral medication, and all patients started on treatment since June have received the drug by mouth. Of the 60 long-term cases, 54 were given oral preparations, either in the form of tablets or as a liquid prepared by mixing the suspension, as supplied for parenteral use, with a flavoured syrup.

Parenteral injections were administered once daily at the beginning of treatment—later, when maintenance dosage was established, they were given either daily or every other day, or, in some cases, three times a week. Because intramuscular absorption is relatively slow, a double dose every other day was found to be just as effective as single doses given each day (Boland, 1950a, 1950b; Freyberg, 1950; Freyberg *et al.*, 1951).

Oral administration has distinct advantages in the practical management of patients; it eliminates the discomfort from injections and allows patients to be independent of others for their medication. In most instances the antirheumatic response is comparable to that resulting from intramuscular injection, but a very few patients, presumably because of faulty alimentary absorption, fail to react satisfactorily to oral administration. Usually the hormone works with greater speed (often within four to six hours) when given by mouth—and the effects wear off sooner. Because the antirheumatic action is rapidly dissipated, more uniform symptomatic control is afforded when the total daily oral amount is taken in divided doses, at fairly equally spaced intervals of six to eight hours.

For convenience' sake, however, most patients took their medication four times each day, at meal-times and before retiring; if the daily maintenance dose was 75 mg., for example, a whole tablet (25 mg.) was taken at breakfast, one-half tablet at noon, a whole tablet at the evening meal, and one-half tablet at or near bedtime. Symptomatic response was not influenced by whether the drug was given before, with, after, or between meals, but tendencies toward insomnia were lessened when a smaller dose was taken at bedtime. In a previous study no constant dosage ratio between the oral and intramuscular routes could be established, but the amounts needed for equivalent relief were surprisingly similar; sometimes the effective doses were the same, but more often oral doses were slightly greater, ranging from one-fifth to one-third more (Boland and Headley, 1951).

Dosage Schedule

The plan of dosage used was prompted by three preliminary observations (Boland and Headley, 1950): (1) The amounts of cortisone needed for effective control varied in individual cases, but, in general, depended more on the severity of the rheumatoid arthritis than on any other single factor—with more severe disease, more cortisone was required. (2) If the rheumatic manifestations were first suppressed by large doses, adequate control could be supported, in most cases, with smaller maintenance doses. (3) The incidence and severity of adverse hormonal reactions were decidedly less when smaller doses of the hormone were used. Regardless of the route of administration, a fairly uniform plan of dosage was followed. This consisted of three stages: (1) period of initial large suppressive doses; (2) period of gradual dose reduction; and (3) period of smaller maintenance dose administration.

Initial Suppressive Doses.—For severe and moderately severe cases 200 or 300 mg. of the hormone was given for one or two days, followed thereafter by 100 mg. daily. For moderate and mild cases 100 mg. was given on the first and subsequent days. These suppressive amounts were continued until the clinical manifestations were brought under control. The period required ranged from 7 to 36 days and in general the time lengthened with the severity of the disease. In a few severe cases amounts of 100 mg. a day were employed throughout because lesser quantities failed to maintain the desired degree of comfort.

Reduction in Dosage.—When rheumatic activity was satisfactorily suppressed with large doses, the daily amounts of cortisone were gradually decreased in a step-like manner. The necessity for gradual reductions was made apparent in some of the early cases which escaped control after the dose was abruptly lowered. The step-down in dosage was made more slowly in severe than in less severe cases. Reductions were usually accomplished at intervals of every four to seven days—by 10 mg. a dose with intramuscular administration, and by 12.5 mg. (one-half tablet) with oral medication.

Maintenance Doses.—Because it was proposed to continue treatment for long periods and because the incidence of unwanted side-effects was greater when large amounts of the hormone were employed, the smallest daily amount which would adequately control the clinical manifestations was considered as the patient's maintenance dose. Attempts were not made to restrain the disease completely, unless this could be accomplished

with relatively small doses, as in some less severe cases. In terms of long-range results it seemed more expedient, as well as more prudent, to be content with satisfactory improvement short of serious hormonal reactions than to strive for total inactivation with large and less safe amounts. Once established, the maintenance dose was continued without interruption. In most cases the amount was not fixed, however, as adjustments in dosage were required from time to time to meet fluctuations in disease activity.

Results of Prolonged Cortisone Administration

Improvement was graded into five categories, as follows: very marked, marked, moderate, slight, and unimproved. The response to treatment was measured by objective and subjective changes in the rheumatic manifestations, increases in functional capacity, improvements in the general constitutional reaction, and corrections of abnormal laboratory findings. The degree of overall improvement was considered satisfactory or adequate if the patient was able to perform his normal business or duties comfortably without analgesics, but perhaps with some restriction in physical activity; this was usually equivalent to improvement graded as very marked or marked.

Overall Results

In 60 of the original 76 patients cortisone administration was carried on continuously for more than six months. Treatment was stopped within the first six months in 16 patients for the following reasons:

(1) In eight patients the response to initial suppressive amounts or large maintenance doses was not sufficient to warrant continuing treatment; improvement was never more than moderate in four, and no antirheumatic effect at all was noted in two (both with spondylitis only). Two patients experienced excellent early results, but after two and four months respectively relapse occurred in spite of increased dosage. Five of the eight patients had very severe disease, and, whereas more benefit might have been realized if massive doses, such as 200 mg. a day, had been given, such amounts would not have been practical for extended use.

(2) In seven patients cortisone was discontinued because unduly troublesome hormonal reactions intervened and doses small enough to avoid them were not sufficient to provide adequate therapeutic results; the disease was graded as severe in five of these.

(3) In one patient complete clinical remission developed after four months' treatment, and administration was stopped. Relapse occurred after five months, and recently cortisone therapy was resumed.

Satisfactory degrees of improvement (very marked or marked) were maintained for periods exceeding six months in 48 of the remaining 60 patients. If the entire group of 76 patients is considered (including those whose treatment was stopped within six months because of poor results or complications and excluding the one patient who developed a temporary remission), it was possible to maintain satisfactory suppression of the disease for long periods (6 to 15 months) in slightly less than two-thirds (48 of 75) of the patients (Table I).

TABLE I.—*Prolonged Cortisone Therapy in Rheumatoid Arthritis: Overall Results in Entire Series of 76 Patients*

Severity of Disease	No. of Cases	Adequate Antirheumatic Control (Very Marked or Marked Improvement) for 6 mths. or Longer	Inadequate Antirheumatic Control but Therapy Continued for 6 mths. or Longer	Reason Cortisone Discontinued before 6 mths.			
				Inadequate Initial Response	Early Deterioration of Improvement	Adverse Hormonal Reactions	Clinical Remission
Severe..	36	17 (47·2%)	8 (22·2%)	5	1	5	0
Mod. sev.	27	19 (70·4%)	4 (14·8%)	1	1	1	1
Moderate	12	11 (91·7%)	0	0	0	1	0
Mild ..	1	1 (100%)	0	0	0	0	0
Total	76	48 (63·2%)	12 (15·8%)	6	2	7	1

General Results in Long-treated Cases

Among the 60 patients treated for periods ranging from 6 to 15 months improvement was graded as follows: very marked in 18 (30%), marked in 30 (50%), moderate in 11 (18.3%), and slight in one (1.7%) (Table II). Thus adequate control was upheld in 48 (80%) of the long-term cases.

In 12 patients (20%) minor and, by our standards, inadequate degrees of improvement were retained. Adverse hormonal effects developed in five of these which subsequently prevented the use of doses large enough to regulate the disease properly. Five others (three with severe and two with moderately severe arthritis) failed to improve more than moderately with continued 100-mg. doses. Two patients were kept under excellent control for 10 and 13 months with quantities of cortisone ranging from 37.5 to 62.5 mg. a day, and then, for unknown reasons, improvement deteriorated; relapse persisted despite increasing daily amounts of cortisone up to 125 mg. a day and intermittent booster doses of 200 mg.

Results in Relation to Severity of Disease

In general, the likelihood of promoting and sustaining major clinical improvement depended more on the severity of the rheumatoid arthritis than on any other single factor. Results were poorer in severe cases because these required continued large, or relatively large, amounts of cortisone which often incited adverse reactions—large but efficient doses often had to be reduced with detriment to clinical results.

Of the 25 severe cases treated for more than six months marked improvement was preserved in 16 and very marked improvement in only one (Table II). Among

TABLE II.—*Prolonged Cortisone Therapy in Rheumatoid Arthritis: Results in Patients Treated Continuously for 6 to 15 Months*

Severity of Disease	No. of Cases	Maintenance Dose Required (mg.)		Degree of Improvement Maintained				Degree of Improvement Considered Adequate		Adverse Hormonal Effects
		Average for Group	Range	Very Marked	Marked	Moderate	Slight	Adequate	Inadequate	
Severe	25	80·5	37·5–125	1 (4%)	16 (64%)	7 (28%)	1 (4%)	17 (68%)	8 (32%)	14 (56%)
Moderately severe	23	64·1	37·5–100	8 (34·8%)	11 (47·8%)	4 (17·4%)	0	19 (82·6%)	4 (17·4%)	8 (34·8%)
Moderate ..	11	55·4	37·5–75	8 (72·7%)	3 (27·3%)	0	0	11 (100%)	0	2 (18·2%)
Mild	1	37·5	37·5	1 (100%)	0	0	0	1 (100%)	0	0
Total ..	60	68·8	37·5–125	18 (30%)	30 (50%)	11 (18·3%)	1 (1·7%)	48 (80%)	12 (20%)	24 (40%)

the original 76 patients the rheumatoid arthritis was graded as severe in 36, and in 11 of these treatment was stopped within six months because of unsatisfactory response or adverse reactions. Thus only 17 of the original 36 severe cases, or less than 50%, were controlled adequately for prolonged periods.

Better results were obtained in patients with less severe rheumatoid arthritis. Very marked or marked improvement was held in 19 of 23 (82.6%) long-term cases, and in 19 of the 27 (70.4%) original cases graded as moderately severe. Satisfactory improvement was maintained in all of the long-term cases with moderate or mild disease, and in 11 of the 12 (91.7%) original cases graded as moderate (Tables I and II).

Size of Maintenance Doses in Long-term Cases

The maintenance requirements for cortisone varied in individual cases and were contingent on several factors. The dose needed for effective control was governed largely by the severity of the arthritis and the amount of physical and/or emotional stress to which the patient was subjected. The average daily maintenance doses in milligrams for the various groups were as follows: severe, 80.5; moderately severe, 64.1; moderate, 55.4; mild, 37.5 (Table II). It should be kept in mind that these figures are for oral administration in the majority of cases (54 of 60) and are probably slightly higher than would be found for a comparable group of patients treated wholly by the intramuscular route. Further, the development of adverse reactions prevented the use of optimal therapeutic doses in some cases; if this had not been so the average amount for severe cases would have been greater.

Stability of Maintenance Doses

The maintenance dose was by no means fixed throughout the course of treatment; in most instances it had to be manipulated from time to time. The natural course of rheumatoid arthritis is subject to fluctuations in activity, and it is reasonable to expect that the dosage requirements of a suppressive drug would vary with oscillations of the disease. Such changes in activity were encountered during treatment; sometimes they occurred spontaneously, while at other times exacerbations were related to some added stress, such as physical overactivity, emotional upset, intercurrent infection, fatigue, etc.

The maintenance dose remained fairly stable, with only minor adjustments being needed periodically, in 36 of the 60 patients (60%).

In nine patients (15%) the dosage remained fairly constant, except that temporary increases in rheumatic activity occurred on one or more occasions which required "booster doses" for the resumption of satisfactory control. Booster doses usually consisted of 100 or 125 mg. of the hormone daily for four or five days, followed by a gradual step-down in dosage to the previous level.

In four patients (7%) the maintenance requirements fluctuated widely from time to time. One patient with moderately severe rheumatoid arthritis, for example, remained very markedly improved for eight months on doses averaging 50 mg. a day. The cortisone requirement then gradually increased and for four months daily doses of 100 to 125 mg. were used. Then, for no apparent reason, the amount called for gradually decreased again, and for the next three months very marked improvement was held on doses of 37.5 to 50 mg. a day.

In five patients (8%) the maintenance dosage gradually increased over the months. The response to initial suppressive therapy was excellent in each instance and adequate control was sustained by smaller amounts for long periods. Improvement then gradually deteriorated and increasing quantities of the hormone became necessary to provide relief. Two patients finally became refractory to even large doses, and eventually cortisone was stopped, after 10 and 13 months of continuous therapy; after a three-months abstinence cortisone was resumed and was again effective in both patients. No reason was evident for the declension of results in three of the five patients, but two ignored advice and assumed additional business responsibilities.

The requirement for cortisone gradually decreased in six patients (10%). In three of them doses as low as 25 mg. a day finally became sufficient, and, with the hope that lasting remissions might have been produced, treatment was stopped after seven, nine, and ten months. Relapse occurred in one patient after seven weeks and in another after two months, while the third is still in remission after three months.

Adverse Effects from Long-continued Cortisone Therapy

Incidence

Twenty-four of the 60 patients (40%) developed undesirable hormonal side-effects at some time during the course of cortisone administration. A single abnormality was presented by 12 patients, whereas the other 12 demonstrated multiple reactions; a total of 45 adverse signs were witnessed in the group (Table III).

In most instances the signs of hormone excess were minor or transient and of little consequence. Of the 45 reactions the severity was graded as mild in 31, moderate in 13, and severe in one (spontaneous fracture). They were sufficiently troublesome to warrant cessation of therapy in only two of the long-term cases (after seven months of administration in one and after 11 months in the other), but their appearance often influenced management of the disease, making temporary or permanent restriction in dosage necessary.

Unfavourable effects were fewer and usually less pronounced when smaller doses of cortisone were used; at the time of their appearance the average daily dose was 75 mg. or more in 17 patients, 62.5 mg. in six patients, and 50 mg. in one patient. Because, in general, the incidence varied directly with the size of the dose, reactions developed most frequently in severe cases and during early suppressive treatment. The number of unwanted effects did not increase greatly with prolongation of treatment; the presently reported incidence of 40% is surprisingly close to that of 35.7% reported in a preliminary study of continuous therapy for periods ranging from two to six months (Boland and Headley, 1950).

Our experience parallels that of others (Freyberg, 1950; Hench *et al.*, 1950a, 1950b; Sprague *et al.*, 1950b; Bunim, 1951), who have noted that undesirable signs are more likely to develop in women than in men. Of the 24 patients exhibiting reactions, 17 were women and seven were men; these represented 44.2% of the 36 women and 29.2% of the 24 men in the long-treated group. Signs of fluid retention, increased androgenic activity, and psychic alterations were more prone to occur in females.

TABLE III.—*Individual Adverse Hormonal Side-reactions in Patients Treated Uninterruptedly with Cortisone for 6 to 15 Months*

Case No.	Sex	Average Daily Dose at Onset (mg.)	Onset of Reaction in Relation to Length of Treatment			Severity of Reaction	Adverse Hormonal Reaction											
			Before 3 mths.	Between 3 and 6 mths.	After 6 mths.		Fracture	Purpura	Pigmentation	Mooning of Face	Skin Tags	Thyroid Enlargement	Nervousness	Oedema	Menstrual Changes	Acne	Hypertrichosis	Dec. Glu. Tolerance
1	M	75·0	•			Mild												•
2	F	75·0		•		,,											•	
3	F	75·0	• (1,2,3,4)			Mod. (1,2,3,4)					• (4)	• (3)	• (2)	• (1)				
4	M	100·0		• (1,2,3,4)		Mod. (1,2) Mild (3,4)			• (4)	• (1)			• (2)			• (3)		
5	F	87·5		•		Mild				•								
6	M	75·0	• (1,2)			Mild (1,2)				• (1)						• (2)		
7	M	100·0			•	Mild				•								
8	F	100·0 (1,2) 62·5 (3,4)	• (1,2)		• (3,4)	Mod. (1,2) Mild (3,4)		• (2)		• (4)				• (1)			• (3)	
9	F	75·0			•	Mild											•	
10	F	100·0	• (1,2)			Mod. (1) Mild (2)				• (2)				• (1)				
11	M	75·0	• (4)	• (1,2)	• (3)	Mild (1,3) Sev. (2)	• (2)			• (1)	• (3)							• (4)
12	F	75·0	• (1)	• (2)		Mod. (1) Mild (2)				• (2)				• (1)				
13	F	100·0 (1) 50·0 (2)	• (1)	• (2)		Mild (1,2)				• (2)				• (1)				
14	F	75·0		• (1,2,3)		Mod. (1,2) Mild (3)				• (1)				• (2)	• (3)			
15	F	100·0			•	Mild								•				
16	F	62·5	•											•				
17	F	62·5		• (1)	• (2)	Mild (1,2)									• (2)		• (1)	
18	M	75·0	•			Mild												•
19	F	62·5			• (1,2)	Mod. (1) Mild (2)				• (2)				• (1)				
20	F	62·5		• (1,2)		Mild (1,2)									• (2)	• (1)		
21	F	62·5	•			Mild											•	
22	F	62·5		•		,,											•	
23	F	50·0			•	,,											•	
24	M	100·0		•		,,				•								

Individual Hormonal Side-effects (Table III)

Changes in Fat Metabolism

Although little is known about the physiological processes involved there is ample laboratory evidence that cortisone may induce alterations in the metabolism of fat. Clinically it has been shown that the hormone may in some cases cause increases in total and esterified serum cholesterol values (Adlersberg *et al.*, 1950) and transient ketonuria (Perera *et al.*, 1949). Apparently the hormone enhances both the absorption and storage of fat, and the distribution of adipose tissue may be so influenced that changes in body configuration similar to those observed in spontaneous Cushing's syndrome may develop.

During the early part of this study diets were unrestricted, and moderate to marked gains in body weight occurred routinely. Generalized obesity became excessive in a few patients and, because of increased appetite and tendency towards fat storage, this was difficult to correct. More recently the caloric intake has been curtailed as soon as the optimal body weight is reached, and excessive gains have been avoided.

Increased deposit of fat in the cheeks, giving rise to rounding of the facial contour, or "mooning," was the most frequent endocrine abnormality noted. It was manifested by 12 patients, nine of whom were receiving relatively large daily amounts (75 mg. or more) of the hormone. The "mooning" usually improved or was corrected by decreasing the dose of cortisone and, if associated with general obesity, by lowering the caloric intake. Two instances of so-called "buffalo hump" due to fat deposit in the back of the neck were noted.

Changes in Carbohydrate Metabolism

Early investigations indicated that cortisone exerts a definite influence on carbohydrate metabolism. When the hormone is administered in large doses to small laboratory animals that are force-fed, hyperglycaemia and glycosuria may be induced (Ingle, 1941), and when given to partially depancreatized animals glycosuria is greatly augmented (Long *et al.*, 1940). Yet, clinically, significant alterations in carbohydrate tolerance are uncommon in non-diabetic patients treated with the hormone. Based on body weight, the amounts of cortisone used therapeutically are relatively small when compared to quantities used to induce a diabetic state in small laboratory animals, and apparently non-diabetic patients have a large functional reserve of islet tissue with which to offset the anti-insulin properties of cortisone (Forsham *et al.*, 1950a). In patients with pre-existing diabetes, however, the diabetes may be intensified, sometimes considerably, during cortisone administration (Boland and Headley, 1949; Brown *et al.*, 1950).

Decreases in carbohydrate tolerance developed in three patients in the present study—one with a normal pre-treatment curve and two with latent diabetes mellitus beforehand. Glycosuria was well controlled in each instance with moderate dietary restriction of carbohydrates (and without insulin) and there was no tendency toward progressive impairment of carbohydrate metabolism in spite of the fact that cortisone was continued for months.

Although the presence of frank diabetes mellitus requiring sizable quantities of insulin for metabolic control appears to be a contraindication to the use of cortisone, clinically mild diabetes need not necessarily prohibit its use. Several patients with rheumatoid arthritis and coexisting mild diabetes, not included in this series, have been cautiously treated with cortisone by us, and sugar metabolism was controlled by the usual diabetic management, employing insulin when necessary.

Changes in Protein Metabolism

Very large doses of cortisone may give rise to increases in urinary nitrogen and the development of a negative nitrogen balance (Sprague *et al.*, 1950b). Diets high in protein, the simultaneous administration of testosterone propionate, and the complemental use of potassium salts have been suggested as measures to circumvent this tendency. Such precautionary steps were not resorted to in the present study, as it seemed improbable that the therapeutic amounts of cortisone used were large enough to cause significant acceleration of protein catabolism.

Changes in Electrolyte Metabolism

Cortisone has a relatively weak sodium-retaining effect, estimated to be about one-thirtieth as great as desoxycorticosterone acetate (deoxycortone acetate *B.P.*) (Thorn *et al.*, 1949). In our experience clinical signs of sodium chloride and water retention usually have not appeared unless relatively large doses of the drug are taken.

Oedema developed in nine patients of this study, all of whom were women, and seven of whom were receiving 75 mg. or more of the hormone each day. Invariably the oedema responded readily to reduction in dosage and dietary restriction of sodium, and diuresis could be hastened by giving saline or mercurial diuretics. During the latter months of the investigation perceptible oedema and sudden weight gains were largely avoided by placing patients on salt-poor diets at the beginning of treatment while initial suppressive doses were given, and by continuing this restriction if maintenance doses greater than 50 mg. a day were employed.

Cortisone is also capable of causing increased urinary excretion of potassium. Instances of potassium depletion from large doses of the hormone, with resultant symptoms of muscular weakness, arterial hypotension, and electrocardiographic changes characteristic of hypopotassaemia, have been reported. Obviously such changes, especially if combined with salt and water retention, could be hazardous in patients with impaired cardiac function. This complication has not been observed in any of our patients, possibly because we have adhered to smaller dosage schedules.

Cutaneous Changes

Alterations of the skin and subcutaneous tissues, like those which occur in Cushing's syndrome and some credited to increased androgen activity, have been observed during cortisone administration. Hypertrichosis was noted in seven women of this series; it was most pronounced on the face, and usually mild, but in two patients it was disturbing and the excessive hair was removed by electrolysis. Two men and one woman developed an acneiform eruption; this cleared spontaneously in one and remained in mild form in the other two. Small papillary skin tags appeared on the necks of two patients and these were removed surgically for cosmetic reasons. Mild purpura, unaccompanied by increased capillary fragility or demonstrable abnormalities in coagulation factors, developed on the lower legs of one patient but disappeared soon after the dose of cortisone was reduced. Slight, but definite, skin pigmentation involving the posterior cheeks and anterior neck occurred in one male patient; this developed early and persisted, but did not intensify despite the fact that he received 100 mg. of cortisone daily for 15 months.

Menstrual Disturbances

Oligomenorrhoea was encountered in three patients, two of whom presented other signs of increased androgen activity (hypertrichosis in one and acneiform eruption in the other).

Skeletal Changes

Cushing's syndrome may be complicated by osteoporosis, excessive calcium excretion, and the development of pathological fractures, especially of the vertebrae and ribs. This suggests that skeletal decalcification and fractures might be provoked by induced hyperadrenocorticalism, particularly when cortisone is given to elderly individuals with pre-treatment osteoporosis.

Spontaneous fractures developed in two of our patients. A 65-year-old man with severe rheumatoid arthritis and spinal osteoporosis beforehand experienced a compression fracture of the twelfth thoracic vertebra after 53 days of treatment. The fracture responded well to orthopaedic management, and cortisone therapy was not discontinued. The second patient, a 66-year-old woman, developed a fracture of the right femoral neck after 34 days of cortisone therapy; no history of injury could be elicited. Open surgical reduction revealed extreme osteoporosis of the femoral head and neck. The possibility of this complication makes one cautious in recommending cortisone therapy for elderly patients, and it would be wise to obtain radiographs of the spine and pelvis for senile osteoporosis routinely in prospective patients over the age of 60.

Psychic Changes

Mental reactions are altered, usually for the better, in most patients who receive cortisone; feelings of well-being are promoted, thought processes are accelerated, attitudes become cheerful, and reprieve from suffering brings hope that crippling may be prevented. In general, the mood is one of elation, and sometimes frank euphoria is encountered which is disproportionately greater than would be expected from the relief of pain alone. Although certain individuals seem to be more susceptible than others, the degree of mental stimulation seems to depend mainly on the size of the dose administered. During the early part of treatment, when large doses of the hormone are being employed, heightened psychomotor activity may be manifest by insomnia, agitation, nervous tension, and increased physical and mental drive. These symptoms usually taper off gradually as treatment is continued and especially after smaller maintenance amounts of the drug are instituted; insomnia and restlessness, for example, are rarely troublesome with daily doses of 75 mg. or less.

Pronounced degrees of mental stimulation occurred transiently in two patients of this series. Both were women in their climacteric who had been emotionally unstable for several years prior to treatment, and in both the symptoms appeared early when large suppressive amounts of cortisone were being given. Other investigators have reported overt psychotic changes coincident with cortisone therapy, but usually there has been evidence of psychopathic disposition beforehand. No instances of real mental depression or maniacal behaviour were encountered in this study; this may be due, in part at least, to the fact that cortisone has been

avoided in patients with psychotic histories or evident emotional instability, and because smaller maintenance amounts of the hormone have been used.

Effects of Prolonged Cortisone Administration on Adrenal Cortical Function

Ingle, Higgins, and Kendall (1938) demonstrated that large doses of cortisone produced regressive changes in the adrenal cortices of rats; cytoplasmic bodies were diminished in size and the cells were depleted of lipoid; the extent of the atrophy resembled that which resulted from anterior pituitary insufficiency in hypophysectomized animals. Subsequently several investigators described in more detail the atrophy produced by large amounts of the hormone. The inner zones of the gland—the zonae fasciculata and reticularis—are principally affected, while the zona glomerulosa is only slightly altered (Stebbins, 1950; Winter *et al.*, 1950). Cholesterol and ascorbic acid concentrations of the glands are reduced. The anatomical alterations so induced are apparently reversible and the cortices are restored to normal size and appearance within 10 to 17 days after cortisone administration is stopped (Winter *et al.*, 1950). Recently Sprague *et al.* (1950a), as well as others (Sokoloff *et al.*, 1951), have demonstrated atrophy of the adrenal cortices, at necropsy, in human subjects treated with large amounts of the hormone for a variety of clinical conditions.

Immediately after cessation of cortisone therapy some patients present symptoms of fatigability and weakness, lasting for varying periods, which have been interpreted as due to inhibited cortical function. During administration the urinary excretion of 17-ketosteroids and the eosinopenic response to a single intramuscular injection of A.C.T.H. are reduced (Forsham *et al.*, 1950b). These changes reflect a depressed functional state of the adrenal cortex. With short-term or relatively short-term therapy the abnormalities have been temporary, however, and after treatment is discontinued the tests revert to normal (Sprague *et al.*, 1950b).

To determine the rate of recovery of adrenocortical function following long-term cortisone administration, the drug was withdrawn in 11 patients included in the present study; they received uninterrupted treatment for periods ranging from 8 to 14 months, and the average maintenance doses of cortisone varied from 37.5 to 100 mg. a day. Withdrawal was accomplished slowly, the daily amounts of hormone being gradually tapered off over periods of 10 to 16 days; this was done in an effort to minimize post-cortisone asthenia and the tendency towards acute articular exacerbations which not infrequently follow sudden cessation of the drug. The response of circulating eosinophils to A.C.T.H. was noted and urinary steroid excretion studies were performed while the usual treatment was being continued, at the end of the period of gradual withdrawal, and at intervals of every one to three weeks thereafter until the determinations returned to accepted normal values.

Details of this study will be reported separately (Boland *et al.*, 1951). In general, the tests indicated that adrenal cortical function was depressed during cortisone administration but that the suppression was not permanent and function returned to normal after withdrawal, even though the hormone was given without interruption for periods up to 14 months. For example, the response of the circulating eosinophils to A.C.T.H. (test of Thorn, Forsham, Prunty, and Hills, 1948) was abnormal in each case during the administration of cortisone—a decrease in eosinophils four hours after a single intramuscular 25-mg. injection of A.C.T.H. either failed to occur or was definitely less than the accepted normal fall of 50%. In 10 of the 11 patients this test gradually improved after cessation of the hormone and reached normal values within periods of 10 to 90 days. In one patient the total eosinophil count before A.C.T.H. was very low, and, although a fall of 50% was recorded on the forty-eighth day, the possibility of experimental error was too great to permit a definite conclusion. It would appear, therefore, that, with the doses given and for the length of administration covered, uninterrupted treatment with cortisone does not produce irreversible functional impairment of the adrenal cortex.

Comment

As clinical experience with cortisone widens doubtless present methods of administration and dosage will be improved upon. Of the various schemes devised and tried so far, however, the uninterrupted method of administration has proved to be the most successful. Our attempts to employ the so-called "course method," which consists of relatively short periods of cortisone administration alternating with intervening rest periods, have not been satisfactory. While improvement has occurred each time the hormone was given, relapse has invariably occurred with interruption of treatment, lasting remissions have not been promoted, and the degree of relapse on withdrawal has not lessened with successive courses. From the standpoint of rehabilitating the arthritic patient for gainful occupation the repetition of alternating relief and relapse has not been practical.

Uninterrupted cortisone administration was effective in controlling the rheumatic manifestations for extended periods in many, but not all, patients with chronic rheumatoid arthritis. Actually it was possible to preserve satisfactory improvement in approximately two-thirds of the cases initially started on treatment. Fluctuations of rheumatic activity commonly occurred during the course of treatment, which required periodic adjustments in dosage, but long-continued administration rarely resulted in refractoriness to the drug. The chief deterrent to successful management was the intervention of objectionable hormonal reactions. Many of the failures were among patients with severe disease whose dosage requirements were large; the quantities needed for proper regulation often provoked unwanted signs of hormone excess, which in turn necessitated a lowering of dosage, often to the sacrifice of clinical improvement.

Unless more effective methods of administration are discovered it is apparent that other measures capable of favourably influencing the activity of the disease will be needed in combination with cortisone if major improvement is to be attained in many patients with severe rheumatoid arthritis. The fact that continued large doses of cortisone almost invariably lead to the development of endocrine complications has prompted a general policy of being content with the best results which can be obtained with smaller maintenance amounts of the hormone, even though only partial rehabilitation is achieved, rather than striving for total symptomatic remission with large and unsafe doses.

With the dosage schedules employed in the present investigations, unwanted side-effects from cortisone

occurred in 40% of cases. This high figure does not give a true picture, however, as most of the reactions were minor and/or transient and of little consequence. The chief disadvantage in their appearance was the fact that they forced a reduction in dosage, often to the detriment of clinical response. The number and intensity of the reactions were greatly reduced when smaller maintenance amounts of cortisone were used. A hormone with less tendency to produce adverse endocrine reactions or one with equal liabilities but greater effectiveness, milligram for milligram, would have advantages in the practical management of patients.

Serious complications during continuous therapy were few and were restricted to patients of the older age group. Vascular thromboses have occurred and have terminated fatally in two patients not included in the reported series; acute coronary thrombosis developed in a 72-year-old man, and cerebral thrombosis occurred in a 74-year-old woman. It seems probable that these complications may have been coincidental with, rather than provoked by, cortisone therapy. More disturbing has been the development of spontaneous fractures in three elderly patients, two of whom are included in the present study. Two of them suffered compression fractures in the lower dorsal spine, and one developed a fracture of the neck of the femur. In each instance the rheumatoid arthritis was severe and of long standing; these factors, in addition to senility, are conducive to osteoporosis, but it is likely that skeletal demineralization was accelerated by the induced state of cortisone excess. Each of the three patients was being maintained on large daily doses (100 mg.) of the hormone when the fractures occurred. More experience will be necessary to determine whether this complication might eventually develop in some younger persons or in those treated with smaller maintenance doses for longer periods than 15 months.

It is now apparent that the depression of adrenal cortical function which occurs during cortisone administration is temporary and the adrenal cortex recovers when the hormone is withdrawn. As judged by steroid excretion studies and the eosinophil response to A.C.T.H., adrenal cortical function returns to normal even after replacement therapy has been given without interruption for periods of up to 14 months. It may be argued that irreversible changes might ensue after cortisone has been administered continuously for longer periods, but this is unlikely. An analogous situation exists in patients with Cushing's disease, when a state of prolonged hormone excess is produced by a unilateral tumour of the adrenal cortex. The contralateral cortex undergoes pronounced atrophy, but after surgical removal of the hyperfunctioning tumour the atrophic cortex recovers functionally and anatomically (Kepler *et al.*, 1948).

Cortisone may be applied successfully as a therapeutic agent in many patients with rheumatoid arthritis, but there are definite limitations to its use. The hormone may be used as a potent antirheumatic weapon, but it probably should be reserved for cases that are resistant to more usual forms of treatment, and, in the light of present knowledge, it should not be considered as the drug of choice for all cases of rheumatoid arthritis. It must be remembered that good results are often attained from more conservative measures and from chrysotherapy. This attitude will be appreciated when it is realized that cortisone does not cure the underlying disease process, that its beneficial influence is only suppressive and is not lasting, and that in instituting it for a chronic disease, such as rheumatoid arthritis, the patient is committed to long and expensive treatment which is not without hazard.

Summary

The administration of cortisone to patients with rheumatoid arthritis usually produces prompt and often dramatic suppression of the disease manifestations. The effects of the hormone do not endure, however, and after withdrawal relapse ensues. For sustained improvement in a chronic disease such as rheumatoid arthritis it appears that cortisone must be given more or less continuously, but its uninterrupted use raises the question of whether administration may be continued effectively and safely for long periods.

Seventy-six patients with rheumatoid arthritis were given cortisone in the hope that treatment could be continued uninterruptedly for extended periods. For various clinical reasons it was necessary to discontinue treatment in 16 of these before six months, but the remaining 60 patients received the hormone uninterruptedly for 6 to 15 months. By using initial large suppressive amounts, then gradually reducing the dosage, and finally employing smaller maintenance doses, adequate degrees of rheumatic control were maintained in approximately two-thirds of the original 76 patients. The ability to maintain satisfactory improvement varied indirectly, in general, with the severity of the rheumatoid arthritis; very marked or marked antirheumatic response was upheld for long periods in 47% of severe cases, 70% of moderately severe cases, and 92% of moderate and mild cases. The chief obstacle to better results in the severer cases was the intervention of adverse hormonal side-effects which developed frequently when large or relatively large maintenance doses were required to support satisfactory improvement.

Unwanted signs of hormonal excess developed in 40% of cases at some time during the course of treatment. Most of them were mild or transient and disappeared or lessened when the dose of cortisone was reduced. The principal objection to their development was that they necessitated a lowering of dosage, which in turn often resulted in clinical deterioration.

During prolonged cortisone therapy evidence of functional suppression of the adrenal cortices, as indicated by a decreased response of circulating eosinophils to exogenous A.C.T.H., was present. The depression of cortical function was temporary, however, and in patients from whom cortisone was withdrawn after 6 to 14 months of continuous therapy tests of adrenocortical function returned to normal within periods ranging from 10 to 90 days.

As experience with cortisone broadens it becomes increasingly evident that there are distinct limitations, difficulties, and dangers in its use in the treatment of chronic diseases. At the present state of our knowledge it appears that cortisone may be employed as a powerful weapon in the management of many cases of rheumatoid arthritis, but it should not be considered as the treatment of choice for most cases, and not as a cure for any case.

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ANTIDIURETIC EFFECT OF NICOTINE AND ITS IMPLICATIONS*

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Antidiuretic Effect of Acetylcholine

Anyone who is prepared to investigate the effects of tobacco smoking lays himself open to the suspicion that he may be a crank and is probably a killjoy. Nevertheless, it must be admitted that the habit of smoking tobacco is widespread, and that the pharmacologist ought to pay some attention to the effects of a drug which is used in greater amount than any other.

Our interest in nicotine began as a consequence of observations made in Edinburgh by Dr. Mary Pickford (1939). She observed that acetylcholine possessed an antidiuretic action in dogs. We know acetylcholine to be the substance which transmits the nervous impulses passing along the vagus to the organs it innervates, and we also know acetylcholine to be a substance liberated in autonomic ganglia, where it transmits the impulse from the pre-ganglionic to the post-ganglionic fibre. The actions which acetylcholine exerts at vagal nerve endings were described by Dale as resembling the actions of muscarine, while those exerted at autonomic ganglia were said to resemble the actions of nicotine. The two kinds of action can be distinguished, as the muscarine actions are abolished by atropine, and in animals under atropine only nicotine-like effects are seen.

Dr. Pickford observed the antidiuretic action by giving dogs water by mouth, and, having also given atropine, she injected acetylcholine intravenously when diuresis was at its height. The antidiuretic action was seen at once and lasted for nearly an hour. She proved that it was due to liberation of the hormone of the posterior lobe of the pituitary, by removing almost the whole of this lobe in some of her animals; in these, only a small fraction of the antidiuretic response to acetylcholine remained. Thus she showed that one of the nicotine-like properties of acetylcholine was to liberate the antidiuretic hormone of the posterior lobe.

Later Dr. Pickford (1947) was able to demonstrate that the site of action of the acetylcholine was the supraoptic nucleus from which nerve fibres pass to the posterior lobe. She accomplished this by making injections of small amounts of acetylcholine (2–40 μg.) directly into the supraoptic nucleus; these caused the antidiuretic action.

The Action of Nicotine

To test nicotine to see if it exerted a similar action was then an obvious step, which we took in the Oxford laboratory (Burn, Truelove, and Burn, 1945). We made observations in groups of rats and showed that nicotine exerted an antidiuretic effect, but failed to do so if rats were used from which the pituitary body was first removed. The amount of nicotine needed to produce the antidiuretic action was large, being 0.16 mg. per 100 g. rat. We had therefore established a point of some slight academic interest.

In view of the dose of nicotine required in the rat it seemed scarcely worth while to test the effect of nicotine in man, and we were greatly surprised to discover that the smoking of one or more cigarettes, according to the sensitivity of the subject, caused an inhibition of the diuresis which followed the drinking of 1 litre of water, and that the antidiuretic action lasted for one, two, or even three hours.

The observations were made on subjects each of whom emptied his bladder at 15-minute intervals. When it was observed that the excretion was regular and less than 25 ml., the subject drank 1 litre. By 45 minutes later the excretion of water had reached perhaps 70 ml. per 15 minutes, and at that point he began to smoke, and was asked to inhale as much as he felt inclined. The inhibition occurred within 10–15 minutes, and in those subjects in whom it was prolonged it was accompanied by toxic symptoms such as pallor, sweating, dizziness, nausea, and sometimes vomiting. These were, however, of short duration, and the period of inhibition outlasted them by two to three hours. When the period of inhibition was shorter, as after smoking one cigarette, it was rare to observe any toxic effects other than transient dizziness and pallor.

Intravenous Injection of Nicotine

To establish that the effect of smoking was due to the nicotine inhaled, we carried out experiments in which the subject did not smoke, but received an intravenous injection of nicotine acid tartrate. We observed that amounts corresponding to 0.33 to 1 mg. of nicotine (as free base) caused an antidiuretic action resembling in duration that due to the smoking of one to three cigarettes. Ling and Wynn Parry (1949) have estimated as a result of a careful study that the amount of nicotine entering the mouth of a smoker from one cigarette is about 1 mg. If it is assumed that about one-third of this is absorbed into the blood stream when the subject

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inhales, we then have fair agreement between the antidiuretic effect of nicotine injected intravenously and of nicotine inhaled through the lungs.

The antidiuretic action of nicotine given intravenously has been studied by Garrod and Cates (1950) in diabetes insipidus; they found that doses effective in normal subjects or those with functional polydipsia were ineffective in diabetes insipidus, and for patients suffering from this disease much larger amounts were required to produce an antidiuretic action.

Mode of Action of Nicotine in Man

The mode of action of nicotine in man is, for the reasons which have already been given, likely to be similar to that of acetylcholine in the dog—that is to say, to be an action due to stimulation of the supraoptic nucleus with resulting liberation of the antidiuretic hormone from the pituitary posterior lobe. Taylor and Walker (1951) have found that an antidiuretic substance appears in the urine after smoking, and have shown that this substance is not nicotine. The substance resembles the hormone of the posterior lobe, inasmuch as it is destroyed by exposing it to the action of N/NaOH for one hour at room temperature. These observations have been confirmed by G. P. Burn and R. Singh Grewal (unpublished), who have shown that the intravenous injection of nicotine also gives rise to the appearance of the antidiuretic substance in the urine.

Thus the evidence that nicotine acts in man in the same way as acetylcholine acts in the dog is strong, and we can conclude that stimulation of the supraoptic nucleus is one of the effects of smoking.

The Vasopressor Hormone

That smoking should release the antidiuretic hormone of the posterior lobe appears at first sight to be of no more than theoretical interest, until it is remembered that this hormone is believed to be identical with the pressor hormone which causes vasoconstriction. In 1928 Kamm and his colleagues separated posterior-lobe extract into two fractions, oxytocin and vasopressin, of which the former possessed the action on the uterus, while the latter possessed the vasoconstrictor action and the antidiuretic action as well. We are therefore faced with the situation that smoking probably liberates in the blood a substance causing vasoconstriction, and must attempt to decide whether the amount liberated may cause constriction of the coronary vessels in the heart.

On this point we have no direct evidence from man to offer, and we are obliged to base our inferences on observations in the dog. We have been able to demonstrate that nicotine has a constrictor action on the coronary vessels of the dog (Bülbring, Burn and Walker, 1949). To do this it is necessary in the first place to arrange that in the anaesthetized animal in which the observations are made the general blood pressure should remain constant. The general blood pressure provides the driving force for the coronary flow, and, unless this pressure is stationary, changes in coronary flow cannot be attributed to changes in the calibre of the coronary vessels.

To ensure a constant blood pressure we attached the femoral artery of the dog to a reservoir of dog's blood (containing heparin). By connecting the reservoir to a 20-litre vessel containing air at a pressure of 130 mm. of mercury, changes of blood pressure in the dog were excluded. When the dog's blood pressure would otherwise have risen, blood was driven out into the reservoir; when the dog's blood pressure would have fallen, blood entered the dog from the reservoir. The dog was given artificial respiration and its chest was opened. A cannula was then inserted through the tip of the right auricle into the coronary sinus, to collect that fraction of the coronary venous blood which issues into the right auricle at that point. It is about 60% of the total coronary flow. This blood was conducted back through a tube to the dog's right external jugular vein, but the rate of flow could be measured at any moment from a T-piece in this tube.

In this preparation we then studied the effect of injecting nicotine into a vein at a uniform rate during a period of 10 minutes. Now it is known from other experiments that the direct effect of nicotine on the coronary vessels is to cause dilatation. In accordance with this we found that the first effect of the nicotine, given in a total of 1.3 mg. to a dog of 15 kg., was to cause dilatation, but that later the dilatation gave place to a progressive vasoconstriction which in 20 minutes reduced the initial coronary flow from, for example, 100 ml. to 93 ml. a minute. This dog was anaesthetized with pentobarbitone sodium, and it is likely that the anaesthetic diminished the effect of nicotine on structures such as the supraoptic nucleus. Thus we obtained evidence of two effects of nicotine on the coronary flow: the first a dilator action presumably due to a direct action on the coronary vessels, and the second a constrictor action supervening later, such as might be due to the release of the posterior-lobe hormone. We were in fact able to imitate this constrictor action by giving posterior-lobe extract intravenously at a rate of 3.3 milliunits a minute.

The Threshold Dose of Posterior-lobe Extract

We carried out a further series of experiments to determine what concentration of posterior-lobe extract was sufficient to cause some vasoconstriction of the coronary vessels in the absence of any anaesthetic. We wished to learn what was the threshold dose. We performed these experiments in the well-known Starling heart–lung preparation in which the central nervous system is excluded, and found that amounts ranging from 5 to 100 milliunits added to a circuit containing about 1 litre of blood produced a reduction in coronary flow in each of the 26 trials, the reduction varying from 2 to 25%.

In 11 trials the amount injected was 20 milliunits and the mean reduction in flow was 13%, this being the effect both when the injection was made into the superior vena cava and when it was first diluted in the reservoir of blood before it reached the heart. From these experiments we learnt that a concentration of 20 milliunits of pituitary (posterior lobe) extract per litre is above the threshold dose necessary to produce coronary constriction. The question then arose whether, in a man who has about 5 litres of blood, smoking would liberate a quantity of 100 milliunits, which would then give a similar concentration of the hormone.

Estimation of Hormone Released by Nicotine

A brief statement has been published by Lewis and Chalmers (1950) of experiments they have made which show that there is a linear relationship between the duration of the inhibition produced in man by graded intravenous doses of pitressin and the logarithmic dose. Having obtained the relation, they observed the duration

of inhibition caused by nicotine and then calculated the amount of hormone liberated by nicotine. They say that study of 21 normal subjects showed that the inhalation of cigarette smoke until severe malaise results releases an amount of antidiuretic hormone equivalent to more than 100 milliunits of pitressin.

Similar observations have been made at Oxford by G. P. Burn and R. Singh Grewal (unpublished). They also found that the period of antidiuretic action is proportional to the logarithm of the dose of posterior-lobe extract given intravenously.

A good many observations have already been made of the duration of the inhibition caused by smoking cigarettes. These are recorded in the Table, which

The Antidiuretic Effect of Cigarette-smoking

Author	Subject	No. of Cigarettes	Inhibition (min.)	Equiv. P.L.E. (milliunits)
Burn *et al.* (1945) ..	L.H.T.	3	210	>1,000
		3	120	190
	E.M.V.W.	3	210	>1,000
		1	105	90
	J.H.B.	1	195	>1,000
	T.H.C.L.	2	180	>1,000
	J.R.W.G.	2	195	>1,000
Walker (1949) ..	A (N)	1	165	>1,000
	B (N)	1	165	>1,000
	C (N)	1	120	190
	D (N)	1	105	90
	E (S)	1	75	18
	F (S)	1	60	7
	G (S)	1	60	7
	H (S)	2	180	>1,000
	J (S)	2	120	190
	K (N)	2	90	40
	L (S)	2	90	40
	M (S)	2	60	7
	N (S)	2	45	3
G. P. Burn and R. Singh Grewal	B	2	105	85
	B	2	105	85
	A	2	195	>1,000
	A	1	105	85

N = Non-smoker. S = Smoker.

shows that the inhibition caused by two cigarettes may be as short as 45 minutes, while at the other extreme the inhibition caused by one cigarette may be as long as 195 minutes. From the relation between dose and effect determined by Burn and Grewal the equivalent dose of posterior-lobe extract which would have produced the same inhibition was calculated, and this dose appears in the right-hand column of the Table. The range of doses of posterior-lobe extract injected to determine the curve did not exceed 1,500 milliunits, and, since it is dangerous to calculate from an extrapolated portion of the curve, the equivalent dose of posterior lobe extract is put down as "$>$ 1,000 milliunits," when the delay indicated the liberation of a greater amount than 1,000 milliunits.

It is important to say that in most experiments in which these large amounts of hormone were released in the blood there were signs of toxic effects such as pallor, sweating, nausea, and occasionally vomiting. If, then, we are to arrive at an estimate of what amount of hormone is released in ordinary smoking, these high figures should be excluded. They leave us with figures ranging from 3 up to 190 milliunits, the figure of 190 milliunits corresponding to the smoking of one, two, or three cigarettes according to the sensitiveness of the individual. The mean of these figures is 75 milliunits, though it is clear that different subjects vary so much that this mean figure has little individual application. Nevertheless, this mean figure indicates that, so far as the evidence goes, amounts of hormone may be liberated in ordinary smoking which are above the threshold for causing coronary constriction.

Practical Conclusions

At this point the scientific evidence ends, at least for the moment, and it remains to consider its practical application, if there is one. Those who train athletes for rowing or cross-country running have long maintained that smoking impairs performance. Probably the evidence now presented accounts for the trainer's view. As few of us, however, are engaged in athletics, the observations scarcely apply to us.

We know little or nothing about the fate of nicotine in the body, but it seems that as we grow older our power to destroy it diminishes. I draw this conclusion from the immunity which many young people seem to have to excessive smoking, and from the observation that many of my colleagues smoke less as they grow older and often stop altogether because they feel it affects their health. There is nothing improbable in the idea that the power to destroy nicotine, which represents tolerance of nicotine, declines with advancing years. If this is so, surely it is clear that those of advancing years who show signs of cardiac irregularity or of coronary involvement should be told not to smoke, because smoking involves some unknown degree of restriction of coronary circulation. We have recently seen evidence from Morris (1951) that during the last 50 years there has been a steady increase in death from coronary disease, which became marked after the 1914–18 war. Of course, that increase can be correlated with many other increases which have occurred in the same period, as, for example, with the increase in the use of motor-cars. However, it is true that in the same period there has been a great increase in the use of tobacco. In 1910 the amount imported which was retained for home consumption was 86,000,000 lb.; in 1942 it was 235,000,000 lb., or almost three times as much. It is possible that smoking is a contributory factor to coronary accidents.

Summary

Smoking, or the intravenous injection of nicotine, can be shown to inhibit a diuresis caused by drinking water in man.

The inhibition is due to the release of the antidiuretic hormone from the posterior lobe of the pituitary, because this hormone is found in the urine after smoking.

This hormone is believed to be the same as vasopressin, which constricts blood vessels, including the coronary vessels.

Nicotine produces a coronary constriction in the dog.

Ordinary smoking of one or two cigarettes liberates in man from 3 to 190 milliunits. Concentrations equal to 100 milliunits in 5 litres of blood are sufficient to cause coronary constriction in the coronary vessels of the dog, and may therefore have the same effect in man.

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THE EXCRETION OF SMALL DOSES OF FOLIC ACID

BY

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AND

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In patients with pernicious anaemia in relapse, synthetic pteroylglutamic acid (P.G.A.) causes reticulocytosis and a rise of the red blood cells and haemoglobin to normal levels. It is an effective treatment for other megaloblastic anaemias. On the other hand, P.G.A. is ineffective against subacute combined degeneration and cannot therefore be used for the routine treatment of pernicious anaemia. It has been suggested, however, that it might be useful as an adjunct to liver therapy. Meyer (1947) reported that a daily dose of 5 to 10 mg. of P.G.A. by mouth, in addition to half a unit of liver extract parenterally, caused a better reticulocytosis than liver alone. Dameshek (1948) claimed that the red blood cells and haemoglobin rose to higher levels when 5 mg. of P.G.A. daily was added to the usual liver therapy, and the patients felt better when receiving P.G.A. Ross, Belding, and Paegel (1948) found that when P.G.A. was substituted for liver extract in maintenance therapy the majority of their patients showed a transitory but significant increase in blood counts, which they thought might be due to the combined effect of P.G.A. and liver extract.

Callender and Witts (1949) found that about a quarter of the patients with pernicious anaemia attending this department required a maintenance dose of 4 ml. of concentrated liver extract ("anahaemin") a week, or about four times as much as is usually thought necessary. In some instances even this dose did not maintain the red cells above 4,500,000 per c.mm., and it seemed possible that the poor responses might be due to a deficiency of P.G.A. Such a deficiency might arise because liver extract increases the urinary excretion of folic acid in pernicious anaemia above the levels found in untreated patients (Bethell, Meyers, Andrews, Swendseid, Bird, and Brown, 1947).

These observations led us to study the excretion of small physiological doses of P.G.A. given intravenously to normal subjects, to patients with steatorrhoea, and to treated and untreated patients with pernicious anaemia. The treated patients with pernicious anaemia included those requiring large doses of liver extract. In this way we hoped to obtain information on the requirement and utilization of folic acid in these groups. Similar studies (Bethell *et al.*, 1947) have been reported with therapeutic doses of P.G.A. These doses are much greater than the normal dietary intake, which is of the order of 60 μg. a day (Denko, Grundy, Porter, Berryman, Friedemann, and Youmans, 1946). With the therapeutic doses a considerable portion of the administered P.G.A. is excreted in the urine, whether or not the subjects have macrocytic anaemia, and little information emerges on the metabolism of folic acid.

Methods

Patients were kept in hospital for the tests. About half of the control subjects, normal young men, were carrying on their usual work in the department: the other controls were hospital patients under treatment for gastric or duodenal ulcers.

Urine was collected for one or more periods of 24 hours before any injections of P.G.A. were given, and then for successive periods of 24 hours after intravenous injections of small doses of P.G.A. A sample of urine from each 24-hour collection was stored under toluene in the cold until assayed. The folic acid content did not change with storage.

Folic acid was assayed with *Lactobacillus casei* ε (*L. helveticus*), using a modification of the method of Roberts and Snell (1946). The urine was diluted and added to the medium, and the folic acid content was read off from a curve relating the amounts of pure P.G.A. used as standards to the bacterial growth measured turbidimetrically after about 40 hours' incubation. A standard curve was obtained with each lot of test samples, and each point in both standards and tests was the average of the opacities found in four individual tubes. Each sample of urine was assayed twice, on different days, and the results are the means

TABLE I.—*Excretion of Folic Acid in the Urine of Normal Male Subjects After Small Intravenous Doses of P.G.A.*

Subject No.	Age	No. of Data for Mean Values in Next Column	μg. P.G.A. Injected: 0·0 (mean value)	50	100	150	200	250	300	350	400	400	400
			μg. Folic Acid Excreted in the Following 24 Hours:										
1*	26					6·7	8·5	8·1	10	12	20		
2	28	1	3·7				4·9	5·5	23	20	22		
13	27	1	10·0					11	20		36		
3	30	4	4·8	4·7	3·0	1·3					13	8·6	
4	27	4	5·6	4·9	6·7	8·2					38	39	49
5	29	4	4·6	4·6	3·7	5·8					25	27	39
Mean response				4·7	4·5	5·5	6·7	8·2	17·7	16	25·7	24·8	44
6	41	2	1·4								9·7	16	18
7	34	2	3·0								7·5	7·1	15
8	42	2	4·3								27	42	40
9	67	2	2·8								6·0	14	18
10	57	2	1·2								3·2	7·4	17
11	25	1	9·9								12		
12	27	1	7·3								22		
1*	26	1	5·2								19		
Mean response											13·3	17·3	21·6

* Both sets of results on Subject 1 refer to one experiment, in which the single dose of 400 μg. in the second part of the table was given on the day before the smaller doses referred to at the beginning of the table.

of the two values. We have referred to the substance injected as P.G.A., for it is pure and defined; the substance assayed in the urine we have referred to as folic acid, and this might include a group of substances which stimulate the growth of *L. casei*.

Studies on Subjects without Nutritional or Blood Diseases

The daily excretion of folic acid without supplements of P.G.A. was between 1 and 10 μg., with a mean between subjects of 4.9 μg. The effect of increasing intravenous doses up to 400 μg. of P.G.A. is shown in Table I. There was no detectable increase in excretion with doses of less than 200 μg., but an increase was always apparent with 400 μg., and some increase usually occurred with intermediate doses. In the later experiments in patients, only the 400-μg. dose was used, given usually on three successive days as before. Further data on normals were therefore collected for the 400-μg. dose, given without previous smaller doses, and the results are shown in the second part of Table I.

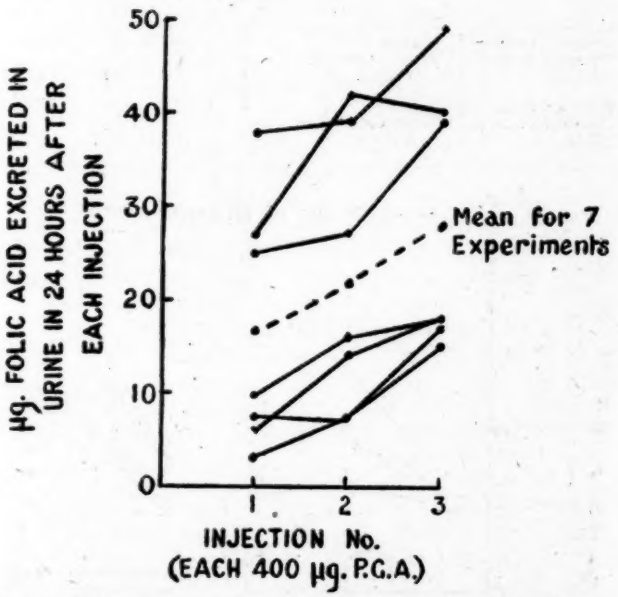

FIG. 1.—Excretion of folic acid in the urine of normal subjects after consecutive intravenous injections of 400 μg. of P.G.A.

From the results it appears that, in spite of the sudden flooding that occurs when drugs are given intravenously, P.G.A. is efficiently utilized when given in amounts up to 400 μg. Even with this amount there is at most a 10% loss in the urine. It is convenient to say that the other 90% is utilized, though this does not mean that its ultimate fate, whether destroyed, stored, or however used up, is known. The amount of folic acid lost in the urine after a dose of 400 μg. of P.G.A. seemed to be greater in the subjects who have been receiving P.G.A. beforehand than in those who had not (Table I). Moreover, in seven subjects who received three injections of 400 μg. of P.G.A. on consecutive days there was an increasing loss of P.G.A. with successive injections (Fig. 1). The mean excretions were successively 16.6, 21.8, and 28 μg. of folic acid. These differences are significant.

To assist in interpreting these data, the pattern of the urinary excretion of folic acid after the intravenous injection of 1 mg. of P.G.A. was investigated in one subject (Fig. 2). Most of the increased excretion occurred soon after the injection, and after six hours the rate of excretion was little more than before the injection. This agrees with earlier findings with larger doses (Jukes, Franklin, Stokstad, and Boehne, 1947). Therefore it is unlikely that the increasing urinary loss that occurred after successive daily injections was due to any delayed excretion after previous doses.

In later work P.G.A. has been given by mouth to normal subjects and to patients with macrocytic anaemia. The amounts of folic acid in the blood and the urine have been measured at short intervals afterwards. The results (Spray, unpublished) show that the amount excreted in the urine depends to a great extent on the level in the blood. The blood level would in turn depend on the rate at which folic acid is utilized, for the amount excreted is only a small fraction of the dose, whether this is given by mouth or intravenously. The results in Table I, therefore, may indicate that in normal subjects P.G.A. is less rapidly utilized after the third than after the first injection of 400 μg. This suggests that normal requirements are fully satisfied with these doses, and *a priori* one might expect that a patient who was deficient in folic acid would excrete

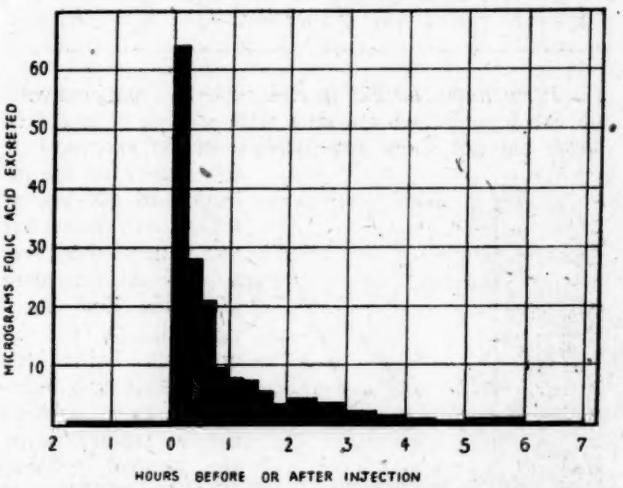

FIG. 2.—Excretion of folic acid in the urine of a normal subject after the intravenous injection of 1,000 μg. of P.G.A.

a smaller proportion of an injected dose than a normal subject. On the other hand, since the normal subject excretes only 10% of the injected dose, it is possible that even a deficient and unsaturated subject could lose as much through the kidneys immediately after intravenous injection while the blood level was still high.

It would be easier to demonstrate a failure to utilize P.G.A. than a deficiency, for then an increase could be expected in the normally small excretion of injected doses. We have tried to interpret the studies in patients in the light of these considerations.

Studies in Patients

1. *Steatorrhoea.*—Two patients with tropical sprue and one with idiopathic steatorrhoea were studied; all had a macrocytic anaemia, which later responded to P.G.A. These patients had a low basal excretion of folic acid, and the excretion was not increased after three successive injections of 400 μg. of P.G.A. (Table II). The test was repeated in one subject after she had been treated with 20 mg. of P.G.A. daily by mouth for six months. Treatment was omitted for two weeks before the test. This time the results were normal.

TABLE II.—*Excretion of Folic Acid in the Urine of Patients with Steatorrhoea After Small Intravenous Doses of P.G.A.*

Case No.	Sex and Age	Condition	R.B.C. (÷10⁶)	μg. P.G.A. injected: 0·0	0·0	0·0	200	300	400	400	400
				μg. Folic Acid Excreted in the following 24 hours:							
1	F 72	Tropical sprue	3·34	1·1	1·9	1·8			1·9	1·5	1·7
1*			4·37		1·7	1·0			30	34	53
2	M 38	Tropical sprue	2·59		0·0	1·5	0·0	3·0	0·9	0·0	2·1
3	M 48	Idiopathic steator-rhoea	2·20		1·1	3·6	0·0	1·2	3·4	2·0	4·4

* Repeated after 6 months' treatment with P.G.A. (20 mg. daily by mouth).

TABLE III.—*Excretion of Folic Acid in the Urine of Patients with Untreated Pernicious Anaemia After Small Intravenous Doses of P.G.A.*

Case No.	Sex	Age	R.B.C. (÷10⁶)	μg. P.G.A. Injected: 0·0	0·0	0·0	400	400	400
				μg. Folic Acid Excreted in the following 24 Hours:					
1	M	65	1·45		9·7	3·7	8·8	5·5	8·9
2	M	53	2·00	0·98	1·7	1·5	2·8	2·1	3·0
3	F	68	1·70		1·8	1·2	2·0	2·1	4·3
4	M	71	1·87	10	12	7·2	21	32	30
5	F	69	1·91		9·1	9·2	28	21	44

2. *Pernicious Anaemia in Relapse.*—Five patients with untreated pernicious anaemia were studied (Table III). Three did not show any increase in the excretion of folic acid after the injection of 400 μg. of P.G.A. In the other two patients there was a normal increase after the first injection, though the increments with the succeeding two injections were perhaps not so regular as in the control subjects (Fig. 3). There is nevertheless an overlap with the normal. The results in steatorrhoea and in some of the patients with pernicious anaemia favour the view that there may be a deficiency of folic acid in these diseases. There is no evidence of any fault in utilization. This interpretation is strengthened by the normal response obtained in one of the patients with steatorrhoea after she had been treated for six months with P.G.A.

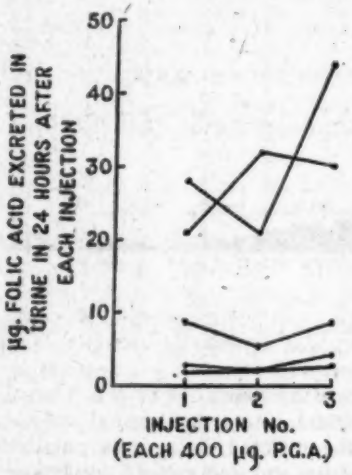

FIG. 3.—Excretion of folic acid in the urine of untreated patients with pernicious anaemia after consecutive intravenous injections of 400 μg. of P.G.A.

3. *Pernicious Anaemia Treated with Liver Extract.*—Thirteen patients were studied who either had not responded fully to small doses of liver extract or had required unusually large doses (Table IV). In seven of the tests smaller doses of P.G.A. (200 and 300 μg.) preceded the 400 μg. doses, and in the rest three injections of 400 μg. were given after the base-line observations had been made. Each group should be compared with the corresponding controls (Table V). The mean responses for patients and controls did not differ, but in two individuals (Cases 9 and 10) the responses

TABLE V.—*Summary of the Urinary Excretions of Folic Acid in Normal Subjects and Treated Patients with Pernicious Anaemia After Consecutive Doses of 400 μg. of P.G.A.*

		No. of Subjects	Mean Excretions of Folic Acid (μg.) in 24 Hours After Each Dose		
Without previous smaller doses of P.G.A.	Normal	7	13·3	17·3	21·6
	Treated pernicious anaemia	6	11·4	20·9	16·4
With previous smaller doses of P.G.A.	Normal	6	25·7	24·8	44·0
	Treated pernicious anaemia	7	16·2	21·7	18·5

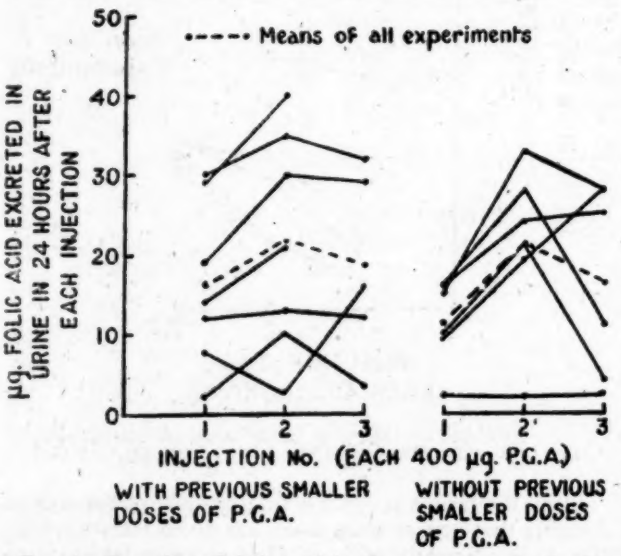

FIG. 4.—Excretion of folic acid in the urine of patients with pernicious anaemia treated with liver extract, after consecutive intravenous doses of 400 μg. of P.G.A.

TABLE IV.—*Excretion of Folic Acid in the Urine of Patients with Pernicious Anaemia Treated with Liver Extract, After Small Intravenous Doses of P.G.A.*

Case No.	Sex	Age	Maintenance Dose of Liver Ext. (anahaemin, ml. per week)	R.B.C. (÷10⁶)	μg. P G.A. Injected: 0·0	0·0	200	300	400	400	400
					μg. Folic Acid Excreted in the Following 24 Hours:						
1	M	68	0·5	4·13	2·3	1·6	2·1	0·6	12	13	12
2	F	82	1·0	4·41	6·5	6·0	3·9	15	30	35	32
3	F	70	1·0	3·88	1·0	1·2	1·3	2·6	7·6	2·7	16
4	M	76	1·0	4·16		3·5	3·3	4·5	14	21	
5	M	64	1·0	4·33	2·5	2·3			16	24	25
6	F	33	2·0	4·28	1·8	2·0	4·0	7·8	29	40	
7	M	56	2·0	4·35	1·5	2·4	3·0	7·8	19	30	29
8	M	74	2·0	5·06	11	9·7			16	28	11
9	M	75	4·0	4·89	0·0	0·0			2·2	2·0	2·3
10	F	81	4·0	4·16	1·5	0·7	0·8	1·4	2·1	10	3·5
11	F	56	4·0	4·60	2·2	1·2			10	21	4·1
12	F	71	4·0	4·37	3·4	1·8			15	33	28
13	M	73	4·0	5·15	0·4	1·1			9·4	19	28

were poor. With successive injections of 400 μg. the patients did not usually show the regular increment in excretion seen in normals (Fig. 4). The results in these patients were thus intermediate between those from normals and those from untreated patients with pernicious anaemia or steatorrhoea.

Discussion

Information derived from studies with vitamin B_{12} has to some extent revised the premises on which the experiments now reported were based. Determinations of the potency of liver extracts and of the maintenance dose of vitamin B_{12} lead to the conclusion that our group of patients under treatment for pernicious anaemia was not, in fact, especially resistant to treatment (Girdwood and Carmichael, 1950; Mollin, 1950). The possibility that vitamin B_{12} may not be a complete therapy for pernicious anaemia still remains, but there is no evidence that such imperfections as have been reported can be corrected by P.G.A. (Beard, McIlvanie, and Nataro, 1950). During the course of these experiments, therefore, our interest has shifted to the more general problem of the metabolism of P.G.A. in health and in the megaloblastic anaemias, and this paper represents our preliminary observations in this field.

The excretion test used was necessarily not sensitive, and interpretation of the results is complicated by uncontrolled factors such as abnormalities of renal function. Nevertheless, the results enable one to speculate a little further on the abnormality of folic acid metabolism in patients with macrocytic anaemia; and the later findings, referred to above, have helped to eliminate some of the uncertainties. Folic acid probably exerts its therapeutic effect because the patients either have a deficiency of the substance or are unable to utilize it properly. Our results favour a deficiency. This could be absolute, due to deficient intake, deficient absorption, or increased excretion; or it could be relative, arising from increased need or increased destruction. Our results do not help in choosing between these possibilities except by excluding an increased excretion of folic acid. They merely indicate that in some patients with macrocytic anaemia the tissues have a great avidity for folic acid. In steatorrhoea, this could be due to an absolute deficiency, while in pernicious anaemia it might be the result of a relative or conditioned deficiency.

Summary

We have attempted to study the utilization of folic acid by measuring the excretion of small doses injected intravenously into four groups of subjects: 10 normal, 3 patients with steatorrhoea, 5 patients with untreated pernicious anaemia, and 13 patients with pernicious anaemia who were under treatment.

In normal subjects there was no increase in the excretion of folic acid in the urine when amounts of less than 200 μg. of P.G.A. were given intravenously. There was an appreciable increase with 400 μg., but the increase represented less than 10% of the injected dose. Hence utilization was good. The amount lost in the urine tended to rise with successive doses of 400 μg.

The patients never excreted more of an injected dose than the normal subjects. Some did excrete less: 3 patients with steatorrhoea, 3 with untreated pernicious anaemia, and 2 treated patients with pernicious anaemia. Others failed to show a rising excretion with successive doses. There was an appreciable overlap between untreated pernicious anaemia and the normal, but all three cases of untreated steatorrhoea showed diminished excretion.

The results suggest that there may be a rapid and increased utilization of folic acid in some instances of megaloblastic anaemia. This implies a deficiency of folic acid, either real or conditioned, but the results do not enable one to say which. Possibly both occur in different groups of cases.

We are grateful to Miss Barbara Mallett for the haematological data on the patients; to Miss Moira Aitken, B.Sc., Miss Beryl Brinkhurst, and Miss Irene Trollope for assistance with the microbiological assays; to Sister Howells and the nursing staff of Collier Ward for their co-operation in the collection of specimens; and to Dr. R. H. Nimmo-Smith (Department of Biochemistry, University Museum, Oxford) for help with the microbiological assay technique.

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THE USE OF PHENYLEPHRINE TO AID AUSCULTATION OF EARLY RHEUMATIC DIASTOLIC MURMURS

BY

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The detection of active rheumatic valvulitis still depends upon auscultation. As such valvulitis is often the only evidence of rheumatic carditis, its early recognition is important. Owing to the well-known difficulty in interpreting systolic murmurs, accurate diagnosis of aortic or mitral valvulitis depends chiefly on hearing an aortic or a mitral diastolic murmur. On first appearance these murmurs are faint, brief, and apt to be overlooked, especially when there is tachycardia. As is well known, mitral murmurs may be intensified by exercise and by certain postures, such as lying on the left side, and aortic murmurs by holding the breath at the end of expiration. These manœuvres seem to accentuate murmurs either by increasing the work of the heart or by bringing the site of turbulence closer to the stethoscope. It has been realized, however, that exercise may mask a mitral diastolic murmur during the period of tachycardia, and is helpful only when the observer concentrates on the phase of cardiac slowing that succeeds it. There seem to be two possible explanations for this: either that bradycardia facilitates auscultatory perception or that the period of slowing down after effort is associated with an increased mitral blood flow per beat. Whatever the explanation, it seemed reasonable to suppose that auscultation might be helped by a drug that slowed the heart rate and increased the stroke volume, such as a pressor agent

which caused carotid sinus slowing. A pressor effect was also desirable so that the efficiency of the aortic valve could be tested against an increased load.

On inquiry the drug that seemed most suitable for the purpose was *l*-1 (*m*-hydroxyphenyl)-2-methylaminoethanol hydrochloride—" phenylephrine " hydrochloride (Boots). This is a synthetic sympathomimetic amine, described by the makers as having an action " intermediate between those of adrenaline and ephedrine." It causes peripheral vasoconstriction and consequent rise of blood pressure, followed by reflex bradycardia, and appears in some ways to resemble *nor*adrenaline. It may be administered by intramuscular or intravenous injection.

Present Investigation

A total of 118 injections were given to 64 patients, chiefly children, ten of whom were non-rheumatic. The dose was usually 0.25 mg. intravenously; but small children received 0.2 mg. and one heavy adult 0.4 mg.

The blood pressure rose sharply and reached its highest level within two minutes; it returned to normal four to eight minutes after the injection. The average increase of systolic and diastolic pressures was 38 mm. Hg and 25 mm. Hg respectively, the range being 10 to 75 mm. Hg for both pressures. The average decrease in pulse rate was 36, the range being 10–72, and the amount of fall being proportionate to the previous heart rate. Both blood pressure and pulse rate responses were similar in normal and rheumatic cases. Continuous electrocardiographic tracings showed that bradycardia first appeared 7–11 seconds after the injection and lasted three to four minutes. Ectopic beats were noted in 12% of cases and were associated with heart rates below 50; one patient developed intermittent nodal rhythm.

Each of the 64 patients was examined by at least two observers before and after phenylephrine. Repeated injections were given to the earlier cases to determine whether the responses were constant, and certain other patients were tested more than once in the course of their illness. Thus 30 patients received two or more injections. Of the 64 patients, 10 were suffering from conditions other than rheumatic fever and had normal hearts, 19 had rheumatic fever or chorea with no clinical evidence of carditis, and the remaining 35 had unquestionable rheumatic carditis.

In the 29 patients without carditis phenylephrine intensified the heart sounds, including the third heart sound, but did not produce aortic or mitral diastolic murmurs.

In patients with carditis phenylephrine greatly intensified any murmur (systolic or diastolic) that was already present, brought out murmurs hitherto undetected, and caused a number of vanished murmurs to reappear; moreover, any difficulty in distinguishing between a heart sound and a murmur was resolved. These 35 cases of rheumatic carditis fall into three groups.

Group 1.—Nine patients, in whom no diastolic murmurs had been detected previously, had such murmurs for the first time during the phenylephrine test (Table I). Five of them have not had the murmur since, but these are recent cases; the other four developed clinical diastolic murmurs subsequently. One of these cases in a recent rheumatic relapse has developed further carditis and is also included in Group 2.

TABLE I.—*Nine Patients Without any Definite Diastolic Murmurs Before Phenylephrine*

Diastolic Murmur First Heard During the Phenylephrine Test	Additional Diastolic Murmur Heard Subsequently
4 aortic	2 aortic
3 mitral	1 mitral
2 mitral and aortic	1 mitral and aortic

Group 2.—Twelve children up to the time of injection had either an aortic or a mitral diastolic murmur, but not both (Table II). Immediately after phenylephrine, both aortic and mitral diastolic murmurs were heard in seven cases, and both murmurs were heard subsequently on routine examination in four of them. Of the five cases in which phenylephrine merely accentuated an existing murmur, only one, after a further seven weeks of rheumatic activity, produced a second diastolic murmur.

TABLE II.—*Twelve Patients With Only One Definite Diastolic Murmur Previously*

Diastolic Murmur Preceding Phenylephrine	Additional Diastolic Murmur During Phenylephrine Test	Additional Diastolic Murmur Heard Subsequently
5 mitral	4 aortic, 1 none	2 aortic
7 aortic	3 mitral, 4 none	2 mitral

Group 3.—Fifteen patients in whom diastolic murmurs had disappeared were investigated within two weeks of that event (Table III). In eight cases both aortic and mitral diastolic murmurs had been heard previously; four of these now had an isolated mitral diastolic bruit, one an isolated aortic diastolic bruit, and three had no murmurs. During the phenylephrine test both murmurs were again heard in seven of the cases, and one of the murmurs reappeared in the eighth. Isolated aortic diastolic murmurs had been heard previously in six cases, and five of these reappeared after phenylephrine. The fifteenth case originally had an isolated mitral diastolic murmur; in this instance phenylephrine produced both an aortic and a mitral diastolic murmur.

TABLE III.—*Fifteen Patients With Previous Diastolic Murmurs, No Longer Heard Over Two to Three Weeks Before Phenylephrine*

Previous Diastolic Murmurs	Diastolic Murmur Preceding Phenylephrine	Additional Diastolic Murmur During Phenylephrine Test
8 mitral and aortic	4 mitral	4 aortic
	1 aortic	1 mitral
	3 no murmurs	1 aortic only, 2 aortic and mitral
6 aortic	6 no murmurs	5 aortic, 1 no murmur
1 mitral	1 no murmur	1 mitral and aortic

In addition 15 of these 35 patients were reinvestigated later, when rheumatic activity had subsided, and previously heard diastolic murmurs were no longer evident. When phenylephrine was given within four to five weeks of the disappearance of a diastolic murmur this murmur was again brought out; but if the interval was longer than five weeks no murmur could be detected after phenylephrine. In three of these 15 patients a single diastolic murmur, either aortic or mitral, had been present during the stage of activity, and phenylephrine had then brought out a second diastolic murmur never heard otherwise; such murmurs could not be heard after phenylephrine during convalescence in two of the cases. In the third case the artificially induced murmur could still be heard after phenylephrine during convalescence and then appeared at a later date spontaneously.

Effects of a distressing nature have been observed only in two cases. One migrainous subject complained of occipital headache for two hours, and the other patient described frontal headache and substernal oppression for two minutes. In neither was there an extreme increase of blood pressure, and after a second injection later the second subject was symptom-free. Apart from one instance of transient " dizziness," no other patient noticed any subjective

changes at all. A transient erythematous flush of the neck and upper chest was observed in four children, and was the only objective side-effect noted in the series.

Discussion

The murmurs brought out by means of phenylephrine usually became audible about three minutes after the injection, and commonly persisted for 15 to 25 minutes. As stated earlier, the maximum pressor response occurred within two minutes of the injection, and the blood pressure returned to normal within four to eight minutes. Bradycardia occurred as soon as the blood pressure began to rise—that is, about ten seconds after the injection—and lasted three to four minutes. It follows that aortic diastolic murmurs induced by the drug do not depend solely upon the height of the blood pressure and that induced mitral diastolic murmurs do not depend solely upon artificial bradycardia. In fact, aortic diastolic murmurs occasionally developed after the blood pressure and pulse rate returned to normal. It is possible that a damaged aortic valve may leak only after an increased load has been carried for a sufficient time; in other words, that valve strain depends not only upon the size of the load but also upon its duration. Indeed, the fact that the phenylephrine murmur may outlast detectable physiological changes has raised the question whether the drug itself might have caused further valve damage; but all such murmurs have been transient, and this possibility seems improbable.

Mitral diastolic murmurs induced by means of phenylephrine may also bear a similar delayed relationship to the known physiological effects of the drug. As they may still be heard clearly for several minutes after the heart rate has returned to the pre-injection level, their detection cannot be attributed to improved auscultatory perception at slow rates. An augmented mitral blood flow per beat, associated with an increased stroke volume, is more likely to be responsible for the murmur. Functional mitral diastolic murmurs in cases of patent ductus arteriosus and ventricular septal defect have been explained in this way. But the time lag again seems to demand the implication of some other factor.

An obvious possibility is that phenylephrine may increase the stroke volume by a direct stimulating action on the myocardium. At the time of writing only a few physiological studies have been made; these have revealed a rise of jugular venous pressure, right auricular pressure, and pulmonary artery pressure, associated with a slight fall in cardiac output and an increased stroke volume. The duration of these changes and their relationship to bradycardia have not yet been determined in our laboratory.

Summary and Conclusion

Phenylephrine, a sympathomimetic drug with a *nor*-adrenaline-like action, has been given to 64 patients, of whom 35 had rheumatic carditis.

Transient elevation of the blood pressure and reflex bradycardia occurred in like degree in both non-rheumatic and rheumatic cases with and without carditis.

Transient aortic and mitral diastolic murmurs were induced by means of phenylephrine in many cases of rheumatic carditis, but never in non-rheumatic patients or in cases of rheumatic fever without carditis.

Aortic diastolic murmurs so induced are attributed chiefly to an increased load from transient hypertension straining a damaged aortic valve, mitral diastolic murmurs mainly to an increased mitral blood flow associated with an augmented stroke volume resulting from reflex bradycardia; but other factors appear to be implicated.

Such murmurs offer clear evidence of valve damage and may be of considerable diagnostic aid.

I am deeply indebted to Dr. Paul Wood for the original suggestion that initiated this work, as well as for all his subsequent encouragement and criticism. I would also like to express my gratitude to Dr. Eric Bywaters for his many helpful suggestions, and to Dr. Gerald Thomas and other colleagues who have assisted at the clinical observations.

EFFECT OF GROWTH HORMONE AND OF CHORIONIC GONADOTROPHIN ON PREPUTIAL GLANDS OF THE FEMALE RAT

BY

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Selye (1951) has recently observed a striking increase in the size of the preputial glands of the female rat treated with growth hormone (somatotrophin, or S.T.H.). He stated: "Preliminary investigations have shown that, under suitable experimental conditions, S.T.H. causes marked preputial-gland enlargement within 48 hours. Perhaps the sensitivity of this test might be further augmented by topical application of S.T.H. We mention these preliminary findings only because of the urgent need for a clinically applicable sensitive bio-assay method for the estimation of S.T.H. in biological fluids. Perhaps they will stimulate others to explore such possibilities."

We have been interested for some years in the question of whether an increase in the production of growth hormone by the anterior lobe of the pituitary gland could account for the well-known abnormalities of the foetus in diabetic and prediabetic pregnancies, as well as for the development of frank diabetes in women in the latter state (Barns and Morgans, 1948; Gilbert, 1949; Barns *et al.*, 1950). It seemed to us, therefore, that if, following Selye's suggestion, a simple and sensitive method for the assay of growth hormone could be based on the increase in the weight of the preputial glands of the female rat, it might be possible to test directly whether the urinary excretion, for instance, of growth hormone in pregnant diabetics was greater than that of non-diabetic pregnant women in comparable circumstances. As it was certain that chorionic gonadotrophin would be present in high concentration in the body fluids with which we should have to deal, it was important that the effects of this hormone on the preputial glands should also be studied, especially since evidence quoted in Selye's paper suggested that the effect might be far from specific for growth hormone. More-

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over, as the preputial glands are accessory sex organs, it would be reasonable to suppose that they would be influenced by hormones produced by the gonads and indirectly, therefore, by gonadotrophins.

Preliminary experiments have been carried out to test these possibilities under the simplest conditions, and though the results are disappointing we have thought it worth while to record them.

Experiment 1

Nine young albino female rats, of weights ranging between 47 and 66 g., were used. Three rats served as controls, three received a daily injection of pituitary growth hormone (Armour and Co. J-21609R) equivalent to 1 mg. each, and three received a daily injection of 100 i.u. of chorionic gonadotrophin each. The injections were subcutaneous and were given for three successive days; on the fifth day the rats were killed. Their weights and the weights of the preputial glands, ovaries, and uteri are given in Table I. (Because of the small numbers of animals, means and ranges, not standard deviations, are recorded.)

TABLE I.—*Experiment 1: Summary of Effects of Growth Hormone and of Chorionic Gonadotrophin on Weights of Preputial Glands, Ovaries, and Uteri of Rats*

Groups		Controls	Growth Hormone	Chorionic Gonadotrophin
Mean body weight (g.)	Before injections	49·2 (47·1–51·3)	59 (52·9–66)	63·1 (59·5–66)
	After ,,	62 (56·5–65·5)	74 (65–83·5)	74·8 (75·5–82)
Mean weight of preputial glands	mg.	25 (20–33)	30·8 (27–34·5)	50·6 (47·5–65)
	mg./100 g. final body weight	40·5 (30·5–52·4)	41·7 (41·3–42·2)	69·3 (60·4–84·5)
Mean weight of ovaries	mg.	21·5 (15–26·5)	22·8 (21·5–25)	57·8 (47–64)
	mg./100 g. final body weight	37·6 (26·8–44·8)	31 (29·2–33·8)	74·8 (58·5–68·1)
Mean weight of uteri	mg.	71 (33–123)	68 (35–100)	187 (164–208)
	mg./100 g. final body weight	113·5 (58·4–195)	88·8 (53·9–120)	241 (200–270)

It is clear that, in the dose used, growth hormone has had no detectable effect on the preputial glands, ovaries, or uteri. On the other hand, chorionic gonadotrophin has resulted in definite enlargement of all three organs. We must therefore conclude that the experimental procedures we have followed would be totally unsuitable for estimating the growth hormone content of a body fluid which also contained chorionic gonadotrophin.

Experiment 2

Although our supplies of growth hormone were very limited, it seemed that an attempt should be made to verify the activity of the preparation, in view of the disappointing results described above. Accordingly, we injected each of two female albino rats with 0.5 mg. a day for seven days, and on the eighth day determined the increase in body weight and the weights of the preputial glands and ovaries. There were also two uninjected controls of similar initial body weights. The results, given in Table II, demonstrate clearly the growth-promoting efficacy of the preparation used, the treated animals showing a mean increase in weight, per 100 g. original body weight, 72% greater than that of the controls. On the other hand, the mean excess of the weights of the preputial glands and ovaries, per 100 g. final body weight, of the treated animals as compared with the controls was 22% and 25.5% respectively. It

TABLE II.—*Experiment 2: Summary of the Effects of Growth Hormone on the Growth and Weights of Preputial Glands and Ovaries of Rats*

Groups	Controls	Growth Hormone (3·5 mg. Over 7 Days)	% Increase in Case of Treated Animals
Initial body weight (g.) ..	209 212	218 214	
Final ,, ,, ...	220 226·5	241·5 235·5	
Mean increase in body weight per 100 g. original weight (g.) ..	6·05	10·4	72*
Preputial glands (mg.)	104 103	122 134	
Preputial glands mg./100 g. final body weight—means ..	46·3	56·5	22
Ovaries (mg.)	70 94	109 110·5	
Ovaries mg./100 g. final body weight—means	36·6	46	25·5

* Note that this is the percentage increase of *weight gained* by the treated animals, not the percentage excess of final body weight over that of the controls. It is therefore not comparable with the two lower figures in the same column, though these, however, are comparable one with another.

therefore seems that daily injections of growth hormone for three days may produce no appreciable effects, whereas a similar total dose spread over seven days will have clear effects; and that the preputial glands are no more sensitive to growth hormone than the ovaries.

Our results do not seem to bear out Selye's suggestion that the rat's preputial gland is likely to prove a *sensitive* test object for the bio-assay of growth hormone in biological fluids, but further conclusions are not warranted by the scanty experimental data we have presented.

Summary

Preliminary experiments to inquire whether the preputial glands of the female rat would be a suitable test object for the assay of growth hormone have not borne out Selye's encouraging view. Chorionic gonadotrophin caused a much greater increase in their weight than did growth hormone, which produced at least as much relative increase in the ovarian weight.

We wish to thank Dr. Irby Bunding, of Messrs. Armour and Co., for providing the growth hormone.

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In his report for 1950 the school medical officer of health for Manchester remarks: "It is sad that the lip-reading class remains small. We know there must be quite a large number of children in the city deaf enough to need this kind of training, but fewer than half those recommended by the doctors at the audiometer clinic avail themselves of the opportunity. While most parents eagerly accept medical treatment for their deaf children, letting them learn lip-reading probably seems to many tantamount to admitting that some deafness is likely to be permanent, and this is more than they can bring themselves to do. It is a great pity, for the partially deaf pupil is gravely handicapped in school and needs all the assistance he can get. He is not deaf enough to be sent to the school for the deaf, and yet cannot do himself justice in an ordinary school. Ideally, he should be attending a class for the hard-of-hearing, where he would find special conditions for the academic part of his education while participating in the games and practical activities of his schoolfellows with normal hearing, and avoiding the disadvantages of being cut off from their society. Until we have such a facility in Manchester the speech clinic must do what it can for those whose parents will allow them to be helped."

THE CLINICAL SIGNIFICANCE OF FASCICULATIONS IN VOLUNTARY MUSCLE

BY

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Spontaneous twitching of the voluntary muscles has aroused the interest of clinicians and neurophysiologists for many years. Despite the classical paper of Denny-Brown and Pennybacker in 1938, and other valuable though less well-known contributions by Ayer *et al.* (1934), Ford (1939), Odom *et al.* (1943), Denny-Brown and Foley (1948), and the earlier observations of Duchenne (1855), of Kny (1888), and of Schultze (1894) on myokymia, the view is still widely held, both in the United States and in Great Britain, that such spontaneous involuntary flickering, if it occurs repeatedly in muscles other than those of the eyelids or periorbital area, and particularly if it occurs in the small muscles of the hand, is indicative of progressive muscular atrophy (P.M.A.).

The terms "fasciculation" and "fibrillation" are still sometimes used synonymously to describe these visible twitchings, and their appearance in the hands, arms, or feet of doctors or medical students may strike terror into these patients' hearts, whereas in the layman the phenomenon may be scarcely noticed, and even if observed is unlikely to provoke alarm in the absence of other complaint. During the past five years we have collected 16 cases, of which no fewer than 10 were in doctors or senior medical students. In all these cases spontaneous fasciculation was occurring repeatedly and was often widespread, and none were in fact suffering from P.M.A. It is of some interest, however, that in every one of the 10 medically trained patients the presenting complaint was of fasciculation, and the overwhelming anxiety thereby aroused concerning the possible diagnosis dominated the picture, whereas the presence of fasciculation had been noticed subjectively by only one of the six non-medical patients.

It has seemed worthwhile to record our observations on this group if only to clarify further a benign syndrome already described, but still apparently too little known to prevent considerable unnecessary distress and apprehension.

The Problem

Our first concern was to identify, measure, and record true fasciculations, as distinct from fibrillation, and to correlate these records with clinical diagnosis. We accepted, and were able subsequently to confirm, the clear differentiation made by Denny-Brown and Pennybacker between these terms. Fasciculations are the gross visible and often palpable and subjectively sensible contractions of a number of muscle fibres supplied by a single motor-nerve filament; in other words, contractions of motor units. Whereas the motor unit is a physiological whole, a fasciculus or muscle bundle is composed of a number of separate motor units loosely knit together on a purely anatomical basis. Clinical fasciculation can involve part or all of a fasciculus—that is, from one to all of its motor units. We were interested in the possible correlation between the extent and duration of such fasciculation and its significance in clinical terms. On the electromyograph the duration of fasciculation varies between 8 and 12 milliseconds, its amplitude between 0.5 and 1 millivolt.

Fibrillation, on the other hand, is produced by the contraction of individual muscle fibres no longer under the control of a motor nerve: it is seen only in conditions involving severance or degeneration of the nerve supply. Such individual contractions are so small that although hundreds are probably occurring together at any one instant, they remain invisible under ordinary skin. In the tongue, however, they can be seen by the aid of a lens and careful lighting. On the electromyograph they last 0.5 to 1 millisecond and are no more than 30 to 60 microvolts in amplitude. They are not usually recordable on an ink-writing oscillograph, requiring special electromyographic techniques with the use of needle electrodes and a cathode-ray screen for their demonstration, though we were able to overcome this difficulty without needle electrodes for clinical purposes, as will be seen. The problem here was to record both fibrillation and fasciculation at the same time if both were present, and again to correlate this with the clinical state.

Method

The normal full clinical history and examination of the nervous system formed the basis of our approach to patients: the mental state and psychiatric history were carefully evaluated. Subsequent follow-up extended from a minimum of seven months to a maximum of six years from the time when the fasciculations were first observed.

Electromyographic studies were made with surface electrodes and an ink-writing oscillograph, storing the electromyographic discharge on to a wire recorder and playing it back at one-fifth normal speed into the ink-writer when the presence or absence of fibrillation was under investigation. The findings in the 16 benign cases were compared with a number of established cases of progressive muscular atrophy or amyotrophic lateral sclerosis.

Results

As has already been stated, all 16 cases forming the subject of this report displayed continuous and often widespread fasciculations; none suffered from any form of P.M.A. The medical patients showed a number of features in common: in nine out of ten the fasciculations had occurred in the small muscles of the hands as well as elsewhere, and had been accompanied by tension, anxiety, fatigue, and some insomnia. In complaining of this the patients stressed their own conviction that their undeniable tension and distress were secondary to apprehension of the diagnosis of P.M.A., with all that this implied: but in every case objective consideration of their recently preceding history and situation revealed other and important sources of emotional disturbance.

In every case the fasciculations had been noticed by the doctor or student concerned and had been a source of great anxiety and misery for some weeks or months before he had been able to bring himself to seek the advice of a colleague. In several cases an electromyographic examination with an ominous or equivocal report—for example, "diphasic spontaneous action potentials . . . consistent with P.M.A."—had added to the

patient's tribulation before the diagnosis had been questioned or the case came under our observation.

With the exception of a case (No. 4) in which there was radiological evidence of arthritis of the cervical spine, none of the medical patients displayed any evidence of structural abnormality, nor of weakness or wasting, whatever. Apart from the fasciculations their clinical picture included the tension, apprehension, and anxiety already mentioned, a tendency to cramps and hyperhidrosis especially of the palms and axillae, some loss of appetite, disturbance of sleep, and tremor of the outstretched hands. They displayed, in fact, the classical syndrome of myokymia as originally described by Kny and by Schultze.

One only of the non-medical group of six patients complained primarily of fasciculation. He was a 36-year-old university professor (Case 13, below). By the time we saw him the ominously guarded nature of the medical opinions he had received, reinforced by his own amateur but highly intelligent researches into the medical literature, had reduced him to a state of iatrogenic alarm and despondency comparable to that of his medical fellow-sufferers. Like them, his was a case of myokymia. The other five patients included four women between the ages of 26 and 40 currently under treatment for anxiety state or mixed affective disorder at the Department of Psychiatry of the Massachusetts General Hospital, and a young man of 22, an engineer, who actually had muscular dystrophy of the distal type described by Gowers. Three brief illustrative case histories are appended.

Illustrative Cases

Case 2.—A 22-year-old medical student noted fasciculations in the small muscles of the left hand. Six months later he noted the same thing in the right hand during the writing of an examination. He made the diagnosis of P.M.A. himself and came to us for an electromyogram. Neurological examination disclosed no abnormality, nor was there any sign of weakness or wasting whatever. Fasciculations could be elicited from both hands after gentle tapping. The electromyogram revealed these fasciculations as coarse and of maximal duration, involving a number of motor units in the fasciculi concerned, and unaccompanied by fibrillation. These are the findings in myokymia. In view of this, and the length and nature of the history in the absence of evidence of atrophy, he was firmly reassured. It is now over a year since he consulted us, and he has had no further trouble.

Case 7.—For about four years a 41-year-old surgeon had noted fasciculations intermittently in the abductor pollicis and adductor digiti quinti of the right hand, particularly during long operations. He happened to see a case of P.M.A. discussed at "grand rounds" and became so afraid that he might have the same disease that, rather informally, he consulted a colleague, who looked at his hands and said that he might well have it. He spent about three months in a state of utter misery and despair, convinced that his days were numbered and waiting for the inevitable atrophy and difficulty in swallowing to appear. Finally he consulted one of us (R. S. S.). Examination showed no neurological changes; there were occasional fasciculations in the intrinsic muscles of both hands, slight tremor of the extended fingers, and some sweating in both hands. The patient stated that when the fasciculations appeared he also felt some discomfort and a "sense of uselessness" in his hands. He is a tense, exceptionally meticulous operator who undoubtedly suffers considerable strain and anxiety during surgical procedures. He was immensely relieved to learn that he did not have P.M.A., and a year later stated that his fasciculations hardly bothered him at all and his morale had entirely changed.

Case 13.—A 36-year-old university professor first noticed fasciculation in the muscles of his right hand following prolonged writing three years before coming under our observation. He was at this time overseas with the U.S. Army. A civilian physician in the area proffered the diagnosis of "creeping paralysis" and set the stage for a long-continued state of anxiety and apprehension. Fasciculations were intermittent, sometimes a month going by without their appearance. Eighteen months later he consulted another physician, who found no atrophy but noted the visible fasciculations, which at times were brisk enough to move a finger. The remainder of the neurological examination was normal. To settle the diagnosis, the doctor ordered an electromyogram of the muscles, putting on the referral slip, "? possibility of P.M.A." The report read: "Diphasic spontaneous action potentials seen in the muscles of the calf and occasionally in the abductor digiti quinti. Consistent with the diagnosis of P.M.A." On the strength of this the diagnosis of P.M.A. was accepted, but eventually a further electromyographic investigation was requested, and in this way he came to us. By this time it was perfectly apparent that he was not suffering from P.M.A., there being no atrophy despite the occasional fasciculations, nor any abnormal neurological findings. He recovered his morale with appropriate reassurance and has remained well.

Electromyographic Studies

The nature of these has already been indicated. They are further illustrated by Figs. 1, 2, and 3. While the simultaneous occurrence of fibrillation and fasciculation

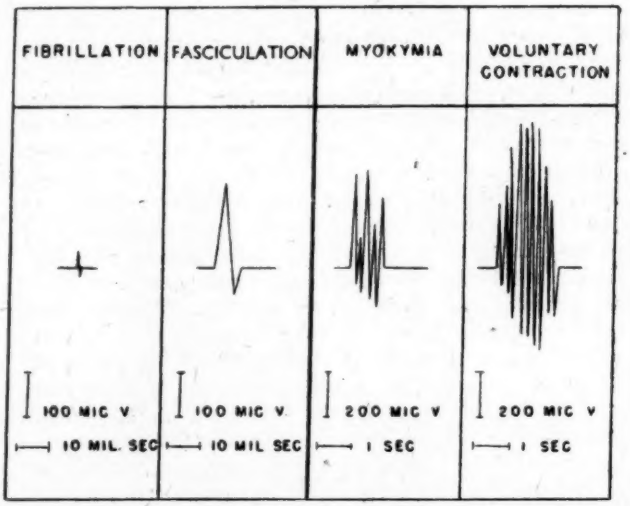

FIG. 1.—Diagrammatic relationship of a fibrillation to a fasciculation and the relationship of myokymia to a voluntary contraction. Note that fibrillation lasts for approximately 1 millisecond and is of low amplitude, whereas the fasciculation lasts for 10 milliseconds and is three to four times the amplitude of the fibrillation. The myokymia is of a shorter duration and lesser amplitude than the voluntary contraction.

in a record must undoubtedly suggest active degeneration, fasciculations by themselves carry no such ominous significance. Furthermore, our clinical impression, based on the modest number of cases at our disposal, tends to confirm the earlier view of Denny-Brown and Pennybacker that the benign fasciculations of myokymia are measurably different from those associated with progressive atrophy; the former being comparatively gross, coarse, and slow and involving most or all of the motor units in a fasciculus, while the latter are more apt to be confined to a small portion of the fasciculus, perhaps a single motor unit, and to be briefer in duration and more rapid in oscillation.

FIG. 2.—This shows the appearance of a fasciculation on an ink-writing oscillograph, and at the bottom part of the picture the same fasciculation is shown in a cathode-ray photograph (right of picture); whereas the fibrillations are indistinguishable on the ink-writer, they show up clearly on the cathode-ray screen.

The use of surface electrodes and a wire recorder to test for fibrillation (Fig. 3) is naturally preferable to needle electrodes for patients who are already anguished and apprehensive.

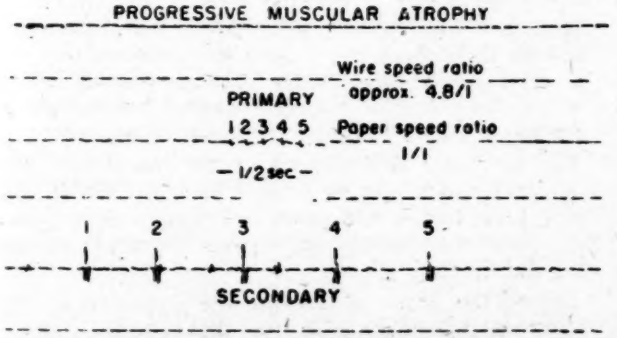

FIG. 3.—By storing the electromyographic discharge on a wire recorder and playing it back at one-fifth the speed into an ink-writer, it is possible to pick up fibrillation without the use of needle electrodes. The third line shows the ordinary recording from a patient with progressive muscular atrophy on an ink-writing oscillograph. Five fasciculations were recorded and are numbered under the word "primary." In the fifth line these same discharges were recorded on the same ink-writer after having been stored in the wire and fed back at one-fifth the speed. The five fasciculations are seen under their numbers, but in addition there are three fibrillations—one before 1, one between 2 and 3, and one between 3 and 4—that were invisible with the ordinary ink-writing technique but were brought out by this method.

Discussion

The occurrence of fasciculations in conditions other than progressive muscular atrophy—for example, thyrotoxic myopathy—is of course widely recognized (Ayer *et al.*, 1934; Starling, *et al.*, 1938; Bartels and Pizer, 1944), although their appearance or exacerbation as a manifestation of emotional tension alone, without any other pathological significance, would seem less well known. While the cause of fibrillation is considered by Denny-Brown and Pennybacker to be an increase in the sensitivity of denervated muscle to normally present acetylcholine, that of fasciculation has been postulated both as a peripheral enhancement of the cholinergic transmitting mechanism at the myoneural junction and a disordered or excessive liberation of acetylcholine at this junction. Odom *et al.* (1943) have even suggested that this local peripheral phenomenon may eventually damage the anterior horn cells and predispose to their degeneration, quoting the findings of Maslard Wigton that antidromic impulses can be traced ascending the motor nerves after fasciculation produced by neostigmine. None the less, they refer in the same paper to a case exhibiting coarse benign and widespread fasciculations over a period of 22 years without ill effect.

Such benign fasciculation may underlie some of the reports of cure or arrest of progressive muscular atrophy by various vitamin extracts, notably vitamin B and *a*-tocopherol (Wechsler, 1940a, 1940b; Stone, 1950; and others). Several of our medical patients had been treating themselves with these preparations, and, had their fears about diagnosis been unrelieved, their subsequent freedom from progressive weakness and wasting might well have been ascribed to an arrest on this basis. Apart from the absence of fibrillation and the preponderance of comparatively coarse fasciculations on electromyography, we have adopted one further clinical criterion in assessing fasciculation as benign: this is its persistence for over three months without the appearance of measurable weakness or wasting. We base this on the observation of Nielsen (1946) that atrophy invariably follows fasciculation "very shortly"—usually within 30 days. Not all clinicians would agree with our inference, however, Odom *et al.* (1943) remarking that in some cases of P.M.A. fatigue and cramps may appear "long before" the onset of demonstrable atrophy.

In conclusion we would emphasize our view that, whereas progressive muscular atrophy or degeneration from whatever cause is a comparatively rare phenomenon, fasciculations in voluntary muscle are not at all uncommon. While they may occur in the entire absence of fatigue or stress and in some individuals are practically a lifelong phenomenon, when accompanied by cramps, sweating, tremor of the outstretched hands, some physical discomfort and emotional tension with subjective fatigue, insomnia, and disturbance of appetite, they form part of the syndrome of myokymia which, to medical patients in particular, is apt to be exceedingly alarming. Their comparatively benign significance, however, can be established by their coarseness and duration, the absence of underlying fibrillation, and their persistence without weakness or wasting of the affected muscles.

With firm reassurance and attention to the psychological and emotional stresses involved, they cease to disturb the patient, although they may never entirely disappear.

Summary

The results of electromyographic and clinical observations on 15 patients with benign fasciculations and one with a distal type of muscular dystrophy are described, and are compared with cases whose fasciculations formed an accompaniment to progressive muscular atrophy. The conclusion is reached that benign fasciculations are

comparatively common, particularly in relation to emotional stress, that they are distinguishable electromyographically from those associated with muscular degeneration, and that patients displaying them can also be differentiated clinically from patients with progressive muscular atrophy at a reasonably early stage. Attention is drawn to the liability of medically trained people to suffer considerable avoidable anxiety in the absence of such distinction being clearly made.

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ACUTE SUPRARENAL INSUFFICIENCY IN PREGNANCY

BY

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Death in the puerperium may be due to many causes, but one of the main "obstetrical" factors is shock occurring at the time of delivery. Death may be immediate but is often delayed, and in these cases it is generally accepted that the cause is either a pituitary necrosis or uraemia due to acute renal damage. From time to time, however, cases occur in which no sign of necrosis can be found in the pituitary and the patients show no evidence of uraemia. Also, there are some patients who die during pregnancy apparently without sufficient cause.

Nine such cases have come under our notice, and in our opinion death was due to acute adrenal insufficiency. Suprarenal haemorrhages are not confined to obstetric practice. They are found in the newborn, and in cases of the Waterhouse–Friderichsen syndrome, which occurs in older children and also in adults. This syndrome consists of fulminating meningococcal septicaemia with massive purpura and bilateral suprarenal haemorrhages. They have also been reported in cases of spontaneous thrombosis of suprarenal veins apart from pregnancy. This, according to Hall and Hemken (1936), is the commonest cause of suprarenal haemorrhage in adults. They also occur in any generalized "haemorrhagic" condition.

In view of the remarkable advances being made in the synthesis of suprarenal hormones it is important that these cases of suprarenal deficiency in pregnancy should be recognized, especially as the damage to the glands does not appear to be irreparable in all cases.

Features of the Syndrome

Although the symptomatology tended to vary, certain features were common to most cases. The syndrome commonly manifested itself by the onset of sudden collapse, the patient exhibiting all the signs of severe shock. Details of the nine cases are shown in Tables I and II, and a description of Case 1 is given below. Three groups of cases could be distinguished by the clinical features preceding the onset of the syndrome: (A) those who developed the syndrome following obstetric shock (Cases 2, 3, and 7); (B) those in whom the illness was ushered in by an attack of late vomiting (Cases 1, 4, 6, and 8); and (C) those in whom pre-eclamptic toxaemia was present before the onset of the syndrome (Cases 5 and 9).

In group A the shock was of haemorrhagic type in all three cases, the causes being accidental haemorrhage (Case 2), post-partum haemorrhage (Case 3), and incomplete abortion (Case 7). The duration of shock varied from 5 to 12 hours, and averaged 9 hours. Prior to the onset of shock two patients (Cases 3 and 7) had been quite well, but one (Case 2) had suffered from bronchitis and debility. These patients recovered from the state of obstetric shock but later collapsed again.

In group B three cases had late vomiting (Cases 4, 6, and 8). The duration of the vomiting before the development of the syndrome varied from 4 to 14 days and averaged 11 days. In Case 4 the vomiting was associated with epigastric pain, and there was a previous history of gastric ulcer. There was associated pyelitis in Case 8, and pre-eclamptic toxaemia was doubtfully present in Cases 6 and 8. The vomiting in Case 1 was slight, but had been continuous throughout pregnancy.

In group C there was definite evidence of pre-eclamptic toxaemia in Cases 5 and 9, and the duration was six and eight weeks respectively. There was no other illness in the antenatal period in Case 6, but in Case 8 there was evidence of pyelonephritis at necropsy.

The syndrome was ushered in by abdominal pain in Cases 1 and 2, and by lumbar pain in Case 4. In Cases 3, 4, and 8 the presenting sign was a rigor. Exhaustion was present just before the onset of the syndrome in Case 1.

During the phase of collapse the condition of the patient was indistinguishable from that of severe shock: the pulse was rapid and weak and at times almost imperceptible; the skin was cold and clammy and the blood pressure low. In Cases 1, 3, 5, and 8 the patient was markedly cyanosed. In their subsequent progress the cases could be divided into two groups.

1. Five patients (Cases 2, 4, 5, 7, and 8) failed to rally from this stage of collapse, and their survival times varied from ½ to 12 hours. During the whole of this period they remained in the same shocked condition, gradually lapsing into coma. In Cases 2, 4, and 7 vomiting developed during the stage of collapse. These five patients did not belong to any single one of the aforementioned groups. In three of these cases there was extensive haemorrhagic destruction of the gland, the central vein was thrombosed in Case 2, and Case 5 showed numerous petechial haemorrhages and marked cellular degeneration.

TABLE I

Case No.	Age	Previous Obstetric History	History and Duration of Present Pregnancy	Condition	Duration of Labour and Delivery	Haemorrhage	Shock	Drugs	Anaesthetics	Transfusions
1	39	11 full-time normal	Vomiting, slight vaginal bleeding. 40 weeks	Retained placenta	13½ hours. Spontaneous	Nil	–	Pituitrin 2 ml.	Nil	Glucose-saline
2	32	4 full-time normal	Bronchitis. 30 weeks	Mixed accidental haem.	2 hours. Spontaneous	+	+ 12 hours	–	–	–
3	23	—	Well. 40 weeks	Post-partum haem.	12 hours. Spontaneous	+	+	Pituitrin 0·5 ml. Ergometrine 0·5 ml.	Nitrous oxide, trilene	Blood, plasma, 20% glucose-saline
4	37	5 full-time normal	Late vomiting. 30 weeks	Late vomiting	–	–	–	–	–	20% dextrose
5	22	—	Pre-eclamptic toxaemia. 38 weeks	–	8 hours. Forceps	–	–	Pituitrin 0·5 ml.	Chloroform	–
6	29	2 full-time normal	Late vomiting. Hypertension. 37 weeks	Late vomiting	–	–	–	–	–	–
7	24	1 full-time normal	Well. 17 weeks	Incomplete abortion	–	+	+ 10 hours	–	Nitrous oxide, ether	Blood, plasma, dextrose
8	?	?	Pyelitis, hypertension, vomiting. 40 weeks	Late vomiting	–	–	–	–	–	–
9	43	4 full-time normal; 4 abortions	Pre-eclamptic toxaemia. 38 weeks	Post-operative vomiting	Caesarean section	–	–	Pituitrin 3 ml.	Spinal procaine	10% glucose-saline

TABLE II

Case No.	Collapse after Delivery		Pain	Vomiting	Cyanosis	Rigors	Oliguria	Paresis	Survival Time	Lesion in Suprarenals
	First	Second								
1	10½ hours	30½ hours	Abdominal	–	+	–	+	–	31½ hours	Massive haemorrhage and necrosis
2	4 days	–	,,	+	–	–	+	–	3 ,,	Central vein thrombosis
3	6 hours	15 hours	–	+	+	+	+	+	21 ,,	Massive haemorrhage and necrosis
4	?	–	Lumbar	+	–	+	–	–	12 ,,	,, ,, ,,
5	5 minutes	–	–	–	+	–	–	Opisthotonos	½ hour	Petechial haemorrhages
6	?	–	–	–	–	–	–	–	7 hours	,, ,,
7	17 hours	–	Headache	+	–	–	–	–	2½ ,,	Massive haemorrhage and necrosis
8	?	–	–	+	+	+	–	–	?	,, ,,
9	?	–	–	+	–	–	–	–	?	Central vein thrombosis

2. Two patients (Cases 1 and 3) made a partial recovery from this stage of collapse. The quality of the pulse improved, cyanosis diminished, and the patient appeared to be relatively comfortable. The duration of this stage was two and four hours respectively, and it was followed by a second and final period of collapse. The terminal phase was of relatively short duration—70 minutes in Case 1 and 5½ hours in Case 3. The condition of the patient at this stage was similar to that in the previous phase of collapse and was indistinguishable from severe shock. There were no prodromal symptoms such as occurred before the first phase of collapse. In Case 3, however, there were additional features which differentiated this patient from all others. During the final phase of collapse she became comatose. In the earlier stages she could be awakened, but her speech was slurred and twitching of the face muscles was noted. Later she became deeply comatose and exhibited spastic movements of the limbs. These movements gradually subsided, and she developed a left-sided flaccid paralysis. It may be mentioned here that in Case 5 of the previous group there was opisthotonos following delivery of the placenta.

In Cases 1 and 3 oliguria was present throughout the illness. This may have been of reflex type and related to the pronounced degree of "obstetric" shock occurring at delivery in Case 3, but in Case 1 there was no "obstetric" shock, and it seems to have been directly related to the condition of the patient in the terminal phase. There was oliguria in Case 2 also, but this was associated with the initial "obstetric" shock and preceded the collapse due to the suprarenal lesion. It is noteworthy that in both Cases 1 and 3 the degree of suprarenal damage was severe.

The remaining two patients could not be grouped as above. In Case 6 the history was deficient, and the patient died shortly after admission to hospital, but there was no evidence of marked shock at any time. In Case 9 the illness was of relatively long duration, and began with vomiting and abdominal distension following caesarean section. This continued until death on the ninth day. During the course of the illness "pituitrin" was given repeatedly. In both Cases 6 and 9 the suprarenal lesions were not gross but were easily distinguishable on microscopical examination.

Additional Factors

Age and Parity.—These did not appear to play any part in the illness. The average age was 31, but individual ages varied from 22 to 43 years. Two were primigravidae (Cases 3 and 5) and six multiparae (Cases 1, 2, 4, 6, 7, and 9). The duration of pregnancy varied from 17 to 40 weeks, the average being 34 weeks.

Duration of Labour and Delivery.—Three patients (Cases 4, 6, and 8) died undelivered, and one (Case 7) had an incomplete abortion which was completed by digital removal. The duration of labour in the three (Cases 1, 2, and 3) who delivered spontaneously varied from 2 to 13½ hours and averaged 9 hours. Case 5 was delivered with forceps after a labour lasting eight hours, and Case 9 was terminated by caesarean section. There was nothing to indicate that the mode of delivery or the length of labour had anything to do with the subsequent illness, except perhaps in Case 9.

Drugs.—Apart from morphine the only drug administered was pituitrin, which was given in Cases 1, 3, 5, and 9; Cases 1 and 9 received large doses.

Anaesthetics.—Nitrous oxide, oxygen, and "trilene" were administered in Case 3, nitrous oxide, oxygen, and ether in Case 7, chloroform in Case 5, and spinal procaine hydrochloride in Case 9.

Transfusions.—Intravenous transfusions of glucose-saline were administered in Cases 1 and 9; 20% glucose-saline or dextrose, plasma, and blood in Cases 3 and 7; and 20% dextrose in Case 4.

General Survey of Features of Syndrome

The onset of the syndrome is sudden and is typified by collapse with a rapid pulse of poor volume and sighing respirations, and may be accompanied or preceded by abdominal or lumbar pain, exhaustion, vomiting, cyanosis, or rigors. Coma, muscle-twitching, and paralysis may occur, but these are unusual features.

The state of collapse may continue for a varying period up to 12 hours until death occurs. In other cases there is recovery from the collapse and the patient is apparently well for a period up to 24 hours, when she once more becomes suddenly collapsed, with rapid feeble pulse, sighing respirations, and increasing cyanosis; this attack proves fatal in a few hours. In the cases that recover from the initial state of collapse there is oliguria during the "lucid" interval.

Arnaud (1900), in his classification of suprarenal haemorrhage in adults, described three clinical types: (1) the peritoneal type with vomiting and abdominal pain; (2) the asthenic type, characterized by asthenia alone, leading to death; and (3) the nervous type in which the patient is found in coma or delirium, and is seen at necropsy to have no cerebral lesion but bilateral suprarenal haemorrhages. Lavenson (1908) and Simpson (1937) add the type in which sudden death occurs from no ascertainable cause and suprarenal haemorrhages are found *post mortem*. These four types were represented in the present series. Cases 1, 2, and 4 were examples of Arnaud's type 1, and Cases 6, 8, and 9 were representative of Arnaud's type 2, while type 3 was exemplified by Cases 3 and 5. Case 7 corresponded with Lavenson and Simpson's type.

The differentiation of the condition from other causes of "acute abdomen" may lead to some difficulty, but from a perusal of Cope's (1940) book it was concluded that the condition most likely to lead to real difficulty in differential diagnosis is acute pancreatitis. Even in this condition there are some differentiating features which will make the diagnosis possible.

Some complicating factor was present during pregnancy or labour in all cases. The associated conditions which occurred during pregnancy were vomiting, pre-eclamptic toxaemia, or pyelitis. The other two patients who were well during pregnancy, however, developed haemorrhagic shock due to some abnormality at parturition. It is possible that large doses of posterior pituitary extract, which is a known vasoconstrictor, may have been a contributory factor in the production of the lesions. Although Cases 4 and 7 developed symptoms during the administration of dextrose it is difficult to imagine that this substance could cause suprarenal thrombosis or haemorrhages.

The syndrome may occur at any age in the reproductive period and in both primigravidae and multiparae. Usually it occurs in the later weeks of pregnancy, but may appear earlier, and either before or after delivery. Blood or plasma transfusion does not seem to play any part in the production of the syndrome.

Post-mortem Findings

The only organs in which significant lesions were detected were the suprarenal glands and the kidneys. The lesions were bilateral in all cases. There were three types of lesion in the suprarenal gland:

Massive Haemorrhage and Necrosis.—This occurred in five cases (No. 1, 3, 4, 7, and 8). There were thromboses in the smaller vessels in all cases, and in two cases (Nos. 1 and 4) there was also thrombosis in the central veins.

Thrombosis of the Central Vein Without Haemorrhage or Necrosis.—This occurred in Cases 2 and 9, although in Case 9 there were a few petechial haemorrhages and the cortical cells were degenerate although not necrotic.

Petechial Haemorrhages in Cortex.—This lesion occurred in Cases 5 and 6: there was no evidence of thrombosis or gross necrosis.

The lesions in the kidneys also varied, but were not gross. In Cases 5, 6, and 9 the changes were those associated with pre-eclamptic toxaemia. In Case 3 there was degeneration of the proximal tubules only, and in Cases 1, 2, and 4 necrosis or degeneration of the proximal and distal convoluted tubules with cytoplasmic debris in the lumina.

The following record is that of a case illustrative of this series.

Case 1

This patient, aged 39, had had 11 previous full-time pregnancies. During each pregnancy she suffered from general debility and sickness. She had no difficult or abnormal deliveries. Throughout the present pregnancy she had slight vomiting and suffered from insomnia. For the four months before admission she had slight intermittent painless vaginal bleeding. She had another slight painless vaginal haemorrhage when 40 weeks pregnant, and was admitted to hospital.

On admission the pulse rate was 98 a minute, respiratory rate 20 a minute, temperature 98° F. (36.7° C.), and the blood pressure 130/70 mm. Hg. There was no albumin in the urine.

The patient remained moderately well, and on the sixth day in hospital the membranes were ruptured artificially. Next day pituitrin was given in doses of 0.5 ml. at half-hourly intervals until a total of 2 ml. had been administered. Two days later a stillborn child was delivered spontaneously after a labour lasting 13¼ hours. The placenta was retained for three hours, but there was no excessive blood loss. The diagnosis of partial placenta praevia was confirmed by examination of the placenta and membranes.

Ten and a half hours after delivery the patient's colour became very poor. She felt exhausted and complained of abdominal pain. The pulse was soft and of poor quality and the rate was 120 a minute. Continuous intravenous saline and glucose was given.

Twenty-eight and a half hours after delivery the patient appeared to be improved, the pulse volume was good, and the intravenous saline was discontinued. Two hours later, however, she suddenly collapsed, the respirations were sighing, and there was increasing cyanosis. She died 70 minutes later. In the first 24 hours after delivery 12 oz. (340 ml.) of urine was obtained from the bladder. There was a terminal rise of temperature to 99° F. (37.2° C.).

Post-mortem Examination

The suprarenal glands were very large and congested and were firmly adherent to the kidneys. There appeared to be haemorrhages into the medulla. The cortices of the kidneys were rather broad and pale. The medullae were also pale, with a few dark streaks in them. In the uterus there was a ring of petechial haemorrhages round the attachments of the Fallopian tubes. There was much gelatinous para-

metrial oedema, and the endometrium was black and foul-smelling. The other organs appeared healthy.

Microscopical examination of the suprarenal glands revealed thrombosis of the central vein, with thrombosis of the smaller vessels and complete necrosis of most of the suprarenal cortex. There were haemorrhages in the cortex, especially in the subcapsular region. In the kidney the glomeruli appeared normal, but there was necrosis of the first and second convoluted tubules and loops of Henle in many areas with altered staining of the cytoplasm and absence of nuclei. In other cases the cytoplasm of the tubular epithelium was degenerate, but the nuclei remained. There was debris in some of the tubules. A few of the collecting ducts showed degeneration and contained debris, but none was necrotic. The afferent arterioles and some of the interlobular vessels were dilated and engorged. There was no significant microscopical change in any of the other organs.

Correlation of Pathological Lesions and Clinical Features

Although all the cases showed a varying degree of adrenal damage this could not be related to a progressive increase in the severity of the symptomatology. The aetiological conditions also varied, but here again no correlation could be found with the degree of pathological change in the suprarenal cortex, except perhaps in Cases 1 and 3, in which the lesions of the suprarenal glands were marked and there was partial recovery from the collapse followed by a second fatal collapse.

The oliguria which occurred in Cases 1 and 3 seems to have been due to necrosis or degeneration in the renal tubules. Whether the necrosis or degeneration of the renal tubules was due to the suprarenal lesions is not clear. In Case 2 the oliguria occurred before the probable onset of the suprarenal lesion; in Case 4 oliguria did not occur even though there was degeneration of both proximal and distal convoluted tubules. It is worthy of note, however, that degenerative changes in the renal tubules have been found in adrenalectomized animals (Simpson and Korenchevsky, 1935), and in many cases of Addison's disease (Barker, 1929). In addition, Marangoni and D'Agati (1944) have reported two cases of Waterhouse–Friderichsen syndrome associated with hepato-renal failure. It has been shown that inulin clearance and diodone clearance are reduced in Addison's disease, and that treatment with deoxycortone acetate partially corrected these deficiencies (Sanderson, 1946–8; Talbott *et al.*, 1942). This is a purely functional derangement, as the azotaemia found in these cases is not to be explained on the basis of structural changes in the kidneys. It is possible that where there is a sudden withdrawal of suprarenal hormones, as in the present series of cases, not only functional but also structural damage to the kidneys is produced.

Literature

Although suprarenal haemorrhages have been fairly often reported with acute infective conditions and a general haemorrhagic state, and in the newborn, there are few cases on record in which suprarenal haemorrhage or infarction has been associated with pregnancy, and in most of them a full account of the pathology has not been given.

Hall and Hemken (1936) reported a case of bilateral suprarenal haemorrhages with thrombi in the veins of the medulla in a young girl who had severe hyperemesis gravidarum. Keele and Keele (1942) gave a very good description of the clinical findings in a case in which thrombosis of the central veins of the suprarenal with infarction and haemorrhage occurred in a woman who was eight months pregnant. Their description agrees in all essentials with the syndrome presented by our first two cases. They also summarize the findings in non-pregnant cases reported in the literature, and there seems to be a similarity in these cases also. A case of massive bilateral suprarenal haemorrhage associated with necrosis of the liver during the puerperium was reported by Dodds (1945). The fourth case, that of Hurter (1946), was one of bilateral suprarenal haemorrhage without thrombosis occurring on the eighth day of the puerperium after a post-partum haemorrhage. In this case there was cloudy swelling in the tubules of the kidneys, and Dodds found degenerative changes in the second convoluted tubules and loops of Henle in her case.

Discussion

Although acute suprarenal insufficiency is a rare occurrence in obstetric practice it is none the less important to be able to diagnose such a condition, as it may now be possible to employ some form of active treatment.

Haemorrhage into the suprarenal glands destroys the tissues and thus prevents formation of the cortical hormones and adrenaline, while thrombosis of the suprarenal veins will prevent the secretion of these hormones. In the absence of these hormones a state of collapse will be easily induced. Hormones of the suprarenal cortex (such as "eschatin") have been used in cases of shock without much benefit, but it is conceivable that in these cases, in which the suprarenals have been damaged, injections of such an extract or some of the more recently isolated hormones would temporarily control the collapse until the suprarenal function was regained. This would apply especially to cases in which there is recovery from an initial collapse followed by a subsequent and fatal collapse. A possible explanation for the two stages of collapse may be that both suprarenal glands are not affected simultaneously in these cases.

The aetiology of the suprarenal lesions remains obscure. It is possible that shock can produce necrosis in the suprarenal glands similar to that produced in the pituitary gland. The vasospasm of pre-eclamptic toxaemia may also have an aetiological role, and a similar condition may be produced by large doses of posterior pituitary extract. Vomiting during pregnancy occurs in a sufficient number of cases to suggest that it is of aetiological significance, but it is not clear how the lesions are produced, though haemoconcentration due to dehydration may predispose to thrombosis.

It was suggested by Keele and Keele (1942) that some cases of Addison's disease might be caused by atrophy or calcification of the suprarenal glands due to old haemorrhage. As some of the cases of suprarenal haemorrhage or infarction were directly or indirectly associated with obstetric shock (Cases 2, 3, and 7, and Hurter's case) it was thought that a follow-up of cases of obstetric shock might produce some support for Keele's suggestion. So far 76 women who had been patients in the Glasgow Royal Maternity and Women's Hospital between the years 1938 and 1941 because of obstetric shock have therefore been followed up. None of the survivors has shown any evidence of suprarenal insufficiency, and none who had died had a history suggestive of Addison's disease.

Summary

Nine fatal cases of acute suprarenal insufficiency occurring in pregnancy are described in which death was apparently due to acute suprarenal insufficiency.

The history of these cases was similar to that described in similar conditions in non-pregnant patients by other authors.

The symptoms of these patients were classified into four groups as described by Arnaud (1900), Lavenson (1908), and Simpson (1937).

The predisposing factors in the cases described appeared to be obstetric shock, pre-eclamptic toxaemia, or late vomiting of pregnancy.

In some cases the pathological lesion was thrombosis of the central veins without destruction of the gland substance, and it is suggested that in these cases the lesion may not be irreparable.

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TREATMENT OF PLANTAR WARTS WITH ELASTOPLAST AND PODOPHYLLIN

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We believe that in recent years there has been a considerable increase in the incidence of plantar warts, though we have no certain evidence of it. Table I shows the increasing numbers of cases seen at the skin department of Edinburgh Royal Infirmary in certain years.

TABLE I.—*Cases of Plantar Warts Seen at the Skin Department, Royal Infirmary of Edinburgh, in 1936–8 and 1948–50*

Year	Cases	Year	Cases
1936	58	1948	168
1937	68	1949	205
1938	105	1950	209

Over 200 cases were seen in 1950, and undoubtedly considerable numbers were also treated by chiropodists, medical practitioners, and consultants in private. Plantar warts are thus common enough to present a problem to every practitioner. They may produce considerable disability, the pain giving rise to a limp and bad posture. If they are left untreated other members of the household may contract the infection, the spread taking place, presumably, from the bathroom floor. Most of the juvenile patients are regular attenders at swimming-baths, which appear to be the main disseminators of the infection.

Since the war much has been written on the dangers or the advantages of the usual methods of treatment of plantar warts. These are in the main radiotherapy, curettage, diathermy, and chemical methods. Their multiplicity indicates that they all have their limitations or shortcomings.

The reports of plastic surgeons (McLaughlin, 1948; Shaw, 1948) on the dreadful sequelae following improper treatment with *x* rays may have aroused prejudice against radiotherapy. This method should be reserved for the solitary wart or for one which is a reasonable distance from others. The mosaic wart—that is, many small warts grouped closely together—should not be treated with *x* rays, and multiple warts should be attacked preferably by other methods.

Diathermy and curettage, or curettage alone, may give good results in the hands of an expert, but the injection of the local analgesic may be rather painful, even with preliminary freezing with ethyl chloride, and there is usually much subsequent discomfort. It is therefore unsuitable for children, who comprise the majority of patients (Table II). The frequent use of general anaesthesia is difficult to arrange in a busy out-patient department.

TABLE II.—*Distribution by Age Groups of 209 Patients With Plantar Warts Seen in 1950*

Age	No.	Age	No.
0–4	6	15–19	32
5–9	34	20–24	18
10–14	97	25 and over	22

The surgical excision of plantar warts usually results in a painful scar, which is often the site of a recurrence. This method should be avoided as a routine procedure.

Various treatments with salicylic plasters and caustics have been described, and are applicable to solitary, multiple, or mosaic lesions. Such measures are often extremely painful, necessitate frequent visits over a long period, and are by no means uniformly successful.

With the introduction of the formalin method (Thomson, 1943) we have the first simple treatment for all types of plantar wart; this is particularly suitable for use in general practice. A fair number of cures can be obtained, but the disadvantage of the method is that the results depend entirely on the thoroughness with which the patient carries out the treatment.

Present Investigation

The treatment described here is equally simple, has proved in our hands more efficient than the formalin method, is applicable to all types of wart, and can be used after failure with *x* rays, surgery, or any other method. By successful treatment we mean here the removal of the substance of the wart followed by an examination three weeks after cessation of treatment to see that no trace remained. Patients were then instructed to report back in the event of any recurrence of symptoms. The "elastoplast" series was completed in October, 1950, and the elastoplast and podophyllin series in January, 1951.

The effects of elastoplast on warts have previously been noted. McAusland (1935) cured two cases of warts on the hands by elastoplast occlusion. Bateman (1942) applied this method to plantar warts and cured nine of seventeen cases: the average duration of treatment was about three to four months. Encouraged by this, we extended this treatment to the majority of plantar warts. The results can be seen in Table III.

TABLE III.—*Cases Treated with Elastoplast Only*

	Duration of Treatment in Weeks									Total
	2	4	6	8	10	12	14	16	18	
Cases cured	0	15	9	18	6	6	2	3	1	60
Cases failed										17
No follow-up										13
Total ..										90

The 17 cases classed as failures fall into two groups. Eight cases had less than two months' treatment with elastoplast before a change of treatment was instituted; this comprised curettage or freezing with carbon dioxide snow, and was used to obtain a more rapid cure. The remainder of the failures were truly resistant, and were treated for more than three months without any benefit.

A study of the histology of the plantar wart will explain the rationale of elastoplast treatment. Its structure is the same as that of a verruca vulgaris. There is considerable elongation of the dermal papillae, with corresponding downgrowth of the rete pegs, which incline inwards at the base and give rise to a cauliflower appearance. In the plantar wart this lies beneath the surface and is usually covered by a thick horny cap, often with a surrounding ring of hyperkeratosis. If this cap can be completely removed pain is relieved and the body of the wart becomes vulnerable to attack by chemicals.

The removal of hyperkeratosis by paring with a knife is very temporary; it soon re-forms. If, however, after paring, the lesion is immediately occluded with elastoplast, any remaining horny material is macerated and its regrowth often prevented. The tenderness of the lesion decreases and its vitality is impaired. If occlusion is maintained continuously for some weeks, a fair proportion, especially multiple small warts, disintegrate. In other cases the papillomatous base becomes visible. This rather resembles a condyloma acuminatum, which is, after all, only a common wart macerated by the natural bodily secretions. It therefore seemed likely that the application of 25% podophyllin in liquid paraffin might be of value. This was in fact shown by Kurtin and Yontef (1948), who first suggested this type of treatment for plantar warts. Their technique consisted of paring down the lesion until bleeding occurred, stopping the oozing with pressure, applying podophyllin, and then covering with adhesive tape to macerate the wart and keep the podophyllin in place. This was repeated at intervals of eight days, and produced 60% of cures.

Podophyllin has proved a very useful adjuvant, and we now use it in all the more resistant cases. It is unlikely to be effective unless the filiform processes of the wart are exposed and it can be absorbed into the body of the lesion. Some four to six weeks' occlusion with elastoplast is usually required before conditions favourable to the use of podophyllin are produced.

Table IV shows the result of this combined treatment. Of the first 40 cases 37 have been cured and three have failed to respond to treatment.

TABLE IV.—*Cases Treated with Elastoplast and Podophyllin*

	Duration of Treatment in Weeks										Total
	2	4	6	8	10	12	14	16	18	Over 18	
Cases cured ..	0	2	6	10	4	7	4	1	2	1	37
Failed											3
Total ..											40

Technique

If the wart has a horny surface it is pared down as far as possible without causing bleeding. If a very sharp detachable scalpel blade is used the lateral pressure on the wart causes little discomfort. Elastoplast is then applied, starting on the dorsum of the foot and carrying it right round and overlapping. When a lesion on the heel is occluded a turn is taken round the ankle. The patient is instructed to report again in two weeks. On the second visit any debris is gently scraped from the surface of the wart, any necessary paring of the wart and surrounding hyperkeratosis done, and the elastoplast reapplied. This is repeated at intervals of two weeks. If the wart does not come away at the second or third visit, podophyllin is started. A small quantity of 25% suspension in liquid paraffin is rubbed in with a glass rod, any surplus dabbed off with wool, and elastoplast applied; paring, podophyllin, and elastoplast are then repeated at intervals of one to two weeks.

If the wart is actively growing and is found to project above the skin surface when the elastoplast is removed, weekly treatment is preferable.

The pressure of the elastoplast on the wart seems an important factor. Lesions on the areas of maximum pressure respond most readily. Warts near the base of the toes may be difficult to macerate and should be covered by a narrow strip of elastoplast extending from the dorsum of the foot and passing between the toes, and then by a band round the foot.

The disintegration of a large wart may be indicated by the sudden onset of tenderness, and when the lesion is pared there is often a discharge of serous fluid, and the centre of the lesion can be pulled out to reveal a red granulating base.

Irritation of the skin on the dorsum of the foot is sometimes produced by the elastoplast, but severe reactions requiring cessation of treatment are uncommon. When a reaction has occurred and the continuation of treatment is desirable, protection of the dorsum of the foot can be afforded by gauze or lint placed between the affected area and the elastoplast.

Podophyllin can produce a severe primary chemical dermatitis and it is also a powerful sensitizer. Little trouble, however, occurs on the thick skin of the sole. It should be used with extreme caution elsewhere, and the skin surrounding each wart should be protected before it is applied.

We have tried the effect of podophyllin on periungual warts on the fingers, after maceration, but owing to the risk of reactions we now prefer to use elastoplast alone in most cases.

Conclusions

The successful treatment of plantar warts requires a knowledge of the special applications and limitations of several methods of treatment. Expert radiotherapy is the treatment of choice for the solitary lesion. In the event of failure with this, or when it is not available, or

in the case of multiple or mosaic warts, it is necessary to resort to treatments of lower efficiency but of wider applicability. Elastoplast occlusion falls into this category; it is safe and is applicable to all types of plantar warts, and certainly deserves to be more widely known.

With this treatment 60% of our cases were cured within two months. This suggests that it should be used as a preliminary treatment.

The series of cases treated with podophyllin and elastoplast shows a higher percentage of cures, but the duration of treatment is about the same. It is emphasized that the podophyllin will not act unless it can be brought into contact with the filiform processes of the wart. It is thus an adjuvant, the main therapeutic agent being the elastoplast. It is possible that as further experience is gained a place will be found for other agents, such as CO_2 snow, liquid air, or formalin bathing, to complete the cure in cases which show a slow response to elastoplast.

We wish to thank Professor G. H. Percival and Dr. G. A. Grant Peterkin for helpful advice and criticism.

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Medical Memorandum

A Case of Typhoid Osteitis Treated with Chloramphenicol

The following case, in which a discharging sinus in the left tibia following typhoid fever was successfully treated with local chloramphenicol after oral chloramphenicol had failed, may be found of interest.

Case Report

An Indian seaman, aged 23, was admitted to the tropical ward of Sefton General Hospital on October 4, 1950, complaining of a painful swelling of the left shin of one week's duration. He said that he had had typhoid fever in Calcutta two years previously, and that three months after leaving hospital he had developed a swelling of his left shin similar to the one of which he now complained. This had broken down and discharged pus. It had been treated with rest and fomentations, and had healed after one month. Thereafter he had remained well and at work till the present recurrence.

On examination a small sinus discharging pus was found at the front of the lower third of the left tibia. The surrounding area was swollen, painful, and tender. The scar of the previous breakdown was seen close to the sinus. Physical examination was otherwise negative. A radiograph of the tibia showed a small area of decalcification in relation to the sinus. Culture of the pus yielded a mixed growth of *Staph. pyogenes* and *Salmonella typhi*, Vi-phage type C. The patient's serum agglutinated *Salm. typhi* H and *Salm. paratyphi* A H at a dilution of 1 in 25 and failed to agglutinate the other standard salmonella suspensions. Repeated cultures of blood, urine, and faeces were negative for typhoid bacilli.

On October 24 a ten-day course of oral chloramphenicol was begun. It consisted of an initial dose of 4 g. followed by 0.5 g. six-hourly. No change in the patient's condition resulted, and cultures taken one week after the course still yielded *Staph. pyogenes* and *Salm. typhi*. On November 27 the sinus and underlying bone were cleaned out surgically, but the wound continued to discharge typhoid bacilli. A second similar course of chloramphenicol from December 15 to December 24 was equally unsuccessful in sterilizing the infection.

On December 29 it was therefore decided to apply chloramphenicol locally, and the contents of one capsule (0.25 g.) were introduced into the sinus daily for 15 days, by which time the wound had healed soundly. The patient was discharged from hospital on February 7, 1951, and was symptom-free when last seen as an out-patient one month later.

Comment

The treatment of intestinal or biliary typhoid carriers with chloramphenicol has been almost uniformly unsuccessful; thus Woodward, Smadel, and Ley (1950) report the complete failure of the drug to cure the four chronic carriers in whom it was tried. In all four carriers *Salm. typhi* did not disappear from the faeces, but it disappeared from the bile during treatment and reappeared shortly after the antibiotic was discontinued. (See also Douglas, 1950; Nina, 1950; Collins and Finland, 1949; Minkenhof, 1949; Rumball and Moore, 1949.)

The only other published case of typhoid osteitis treated by this antibiotic is that of Morse and Geiser (1950), who, writing of a case of typhoid osteomyelitis of the humerus, remark that response was not dramatic but was followed eventually by a cessation of all manifestations during a follow-up period of five months. As the patient had had a previous symptom-free interval of six months it is clear that a permanent cure was not definitely established.

The present case falls into line with the intestinal carriers as regards the failure to respond to oral chloramphenicol. That the local application of chloramphenicol caused the healing of the sinus cannot be said, but it would seem to be a rational procedure in the case of readily accessible typhoid lesions.

I would like to express my thanks to Dr. A. R. D. Adams, under whose care the patient was treated, and to Dr. Carl Brundret for the laboratory investigations.

H. M. GILLES, M.D., D.T.M.&H.

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During 1950 140 British nurses had appointments arranged for them in hospitals abroad, and similar arrangements were made for 260 foreign nurses to work in hospitals in England and Scotland (*Report for 1950*, Royal College of Nursing). Approximately 300 nurses from the Dominions visited the College, and many were helped to find work in hospitals. During the summer many British nurses went abroad with letters of introduction to nurses' associations, and were able to see how hospitals in Europe and Scandinavia are organized.

Reviews

INSECTS

Insects and Hygiene. The Biology and Control of Insect Pests of Medical and Domestic Importance in Britain. By James Busvine, Ph.D., D.Sc. (Pp. 482; 58 illustrations. £1 10s.) London: Methuen and Co. 1951.

Dr. Busvine's book will be welcomed by all who are called upon to identify insect and arachnid pests or to give advice on their control. It fills a long-standing gap in the literature. The author has assembled a large volume of information, including much that has accumulated in the years since 1939 and has hitherto been scattered through a very wide range of journals, many of which are not readily available.

The first four chapters (Insects and Hygiene; Structure and Classification of Insects; Anatomy and Physiology of Insects; Ecology of Insects) compress into 70 pages a mine of information concerning the biology of the arthropods sufficient to enable non-entomologists to understand the later chapters. Then follow three chapters on the principles of control. Dr. Busvine's researches on this subject have contributed much to our understanding of the problems involved, and it is therefore not surprising that this section gives a particularly valuable summary of the present state of our knowledge. A chemical appendix provides details of some of the methods for estimating the most commonly used insecticides, together with an index of insecticides, emulsifiers, and repellents. This index indicates the compositions of commercial preparations and should be especially useful to organizations buying large quantities of such chemicals. The author very properly points out that there should be legislation requiring manufacturers to state the ingredients of the insecticides they sell. There is little doubt that some of the preparations on the market are of limited utility and are excessively expensive.

The remaining chapters are on houseflies and blowflies, bloodsucking flies, parasites, pests of foodstuffs, insect pests and waste products, clothes moths and carpet beetles, wood-boring beetles, and stinging and biting insects. The arthropods mentioned are described and often figured, and the author gives an account of their importance, biology, and control. The material is well arranged, and the information which one requires is readily found, together with extensive references to original papers. A biological appendix gives notes on the preservation and dispatch of specimens and keys for the identification of domestic insect pests.

It is to be hoped that in a second edition of this book insects of veterinary importance will be considered in greater detail and perhaps be given a separate chapter. There is—as indeed is inevitable—some reference to such insects, but, although *Gasterophilus* is mentioned as a cause of larva migrans, there is no mention of *Hypoderma*, which may cause the same condition and is of such importance to the hide industry in Britain. In the section on the mechanism of insect bites the author might well have referred to the histology of the lesions produced and to the topical use of antihistamine drugs in the alleviation of the irritation due to such lesions.

FERGUS J. O'ROURKE.

AROMATIC RINGS

Biological Oxidation of Aromatic Rings. A Symposium held at the London School of Hygiene and Tropical Medicine, November 12, 1949. Organized and edited by R. T. Williams. Biochemical Society Symposia No. 5. (Pp. 95. 8s.) Cambridge: At the University Press. 1950.

The Biochemical Society continues to hold symposia on special topics and to publish an account of them. This is the fifth of the series, and the symposium was arranged by Professor R. T. Williams, who also edited the published account. The subject is one about which surprisingly little is known as yet. As Professor J. W. Cook points out in his introduction, biological oxidation often attacks centres in cyclic molecules other than those which are the most reactive centres towards chemical reagents *in vitro*. Modern views on the mechanism of enzyme action perhaps render this less surprising than might otherwise be the case, but such a situation does not render the elucidation of the biological process any easier.

The general conclusion may be drawn that the oxidation of aromatic rings is often preceded by the introduction of hydroxy groups, often in *ortho* positions. Study of the metabolism of carcinogenetic hydrocarbons and substances related to them illustrates this point very clearly (J. N. Smith, L. Young, E. Boyland). The light thrown on the conversion of saturated or partly saturated ring systems to aromatic rings is discussed by F. Dickens, while F. C. Happold reviews the oxidation of aromatic rings by micro-organisms.

Although no general conclusion can yet be reached, the significance of the metabolism of aromatic rings for cancer, steroid-hormone action, and sterol metabolism cannot be doubted, and it is of importance to have an interim report from experts. It is to be hoped that the Biochemical Society will continue to publish these valuable accounts of discussion on current research by those actively engaged in investigation.

F. G. YOUNG.

STRUGGLES AND ACHIEVEMENTS

In a Harley Street Mirror. By R. Scott Stevenson. With drawings by the author. (Pp. 278. 15s.) London: Christopher Johnson.

Those who enjoyed the author's *Morell Mackenzie* (and they were very many) will welcome this new book by Scott Stevenson. The book is largely but not wholly autobiographical. In the preface the author states that it was at first intended to be a collection of essays and occasional articles, but it gradually developed into an autobiography. Of the 14 chapters the first 6 give a delightful account of the author's early struggles and achievements. He is well known as a specialist in otolaryngology, but he is here revealed as an enterprising and capable editor and journalist, as an artist, a Parliamentary candidate, a traveller, and a man possessing a keen sense of humour. Everyone who likes a good story should read pages 70 and 71 of this book.

The later chapters are interesting and readable, but have not quite the same vital spark which brightens up the early chapters. There are dozens of vivid pen pictures of famous doctors in Great Britain and America, and the reader will be interested to see with what skill the author was able to get *en rapport* with so many different types of person.

We wish that he had inserted a photograph of himself *in* the book; we have been compelled to cut out the picture on the dust-cover and paste it inside the book.

ZACHARY COPE.

PHOTOGRAPHS FOR PUBLICATION

The Preparation of Photographic Prints for Medical Publication. By Stanley J. McComb, F.B.P.A. (Pp. 70; 41 illustrations. 15s.) Oxford: Blackwell Scientific Publications. 1950.

"A good medical photograph combines a high degree of technical perfection with artistry in handling the subject so that information is presented most effectively." Quoted in the introduction, this remark covers the author's intentions, and from it he proceeds through the practical stages of focus, scale and position, background, and lighting to discuss the more imponderable features such as emphasis, improvement of the quality of an imperfect print, and the trimming and grouping of material in order to make the best use of the page.

The book is readable and the author obviously knows his subject (he is in charge of the section on photography at the Mayo Clinic), but to the reviewer it seems that it may well miss its target. In the larger hospitals and medical schools, where there are departments of illustration, Mr. McComb will be preaching to the converted; the smaller centres, where occasional photographic work is done as a part only of the work of a radiographer or laboratory technician, stand in greatest need of his sound advice. Yet it is just these who do not buy photographic books. Perhaps, if the supervisors of such workers read this notice, they will rectify the matter; for if the author's precepts were universally followed the standard of illustration in medical journals would be immeasurably raised and the editors' headaches would be greatly lessened.

Mr. McComb almost disarms criticism by denying that he is writing a textbook; yet, while his intentions are wholly admirable, his own presentation may perhaps be criticized. Marking of figures with disks of white paper apparently made with a filing punch is untidy. Such figures may best be inserted by the blockmaker. Wire paper-clips should *never* be used, even with care, for their indentations will inevitably record on the block. In most British centres all clothing is removed which would appear in the print, and it is generally agreed that a half-clothed figure looks more naked than one completely unclothed. The notably unnecessary socks in Fig. 2d are a case in point. (Fortunately we are not faced with the tricky American legal position in such matters.) The comparable pair of pictures in Fig. 4b are not identically lit, while in Fig. 5a the use of a transilluminated background would produce an entirely shadowless hand. In the chapter on lighting the author treats of a number of detailed methods but dismisses the photography of specimens in four lines, yet this kind of photography provides a large proportion of published work and is generally as badly done as any. The section on improving print quality may be read with advantage by all, for all have at some time had to make do with an imperfect negative which was unrepeatable.

In Britain the trimming and grouping of prints tend to become an editorial function. The final chapter on this subject, if read by all who intend to publish their work, would ease the burden on the editor, who is probably only too ready to accept sound ideas on layout from his authors, but who normally finds them devoid of any ideas at all. The criticisms are of detail only. The book as a whole will be of great value if the publishers can get it into the right hands. The illustration departments will sigh gently and wish the author luck.

ROBERT OLLERENSHAW.

HISTORY OF SCIENCE

The History of Science. Origins and Results of the Scientific Revolution. A Symposium of Broadcast Talks by Sir Lawrence Bragg and Others. (Pp. 184. 8s. 6d.) London: Cohen and West. 1951.

Not long since, the history of science was the very Cinderella of the humane studies. To-day it would be a bold and industrious man who would undertake to read all that is being written on the subject, even in the English language. The output in German, French, and Italian is almost as impressive. The subject has entered the university curriculum and is beginning to penetrate into that of the schools. These sixteen broadcasts by distinguished exponents, each on his own special discipline, were addressed to boys and girls of sixth-form level during the winter session 1949–50. They have been brought into book form and equipped with a useful introduction and bibliography by Dr. Jean Lindsay, of Girton College, herself an enthusiast for the subject. Together they make a most attractive little volume.

The medical reader may well find his special interest in just those wider themes that are peripheral rather than central to his own studies, such as the discussions, "Why was Science Backward in the Middle Ages?" by Professor M. Postan, "Bacon and the Experimental Method," by Professor C. D. Broad, "The Development of Scientific Instruments in the Seventeenth Century," by Dr. Samuel Lilley, "The Birth of Modern Chemistry," by Dr. D. McKie—all admirable writers who are at their best in simplifying the presentation of their subjects for young listeners. The authors who deal directly with medical subjects are Sir Henry Dale on "Harvey and the Circulation," and the Editor of the *British Medical Journal* on "Pasteur and Problems Presented by Bacteria." The chapters of both of them are, as we should expect, models of their kind. Of special interest is the article by the Director of the Science Museum on "Scientific Developments of the Early Nineteenth Century," for he provides a partial explanation of why medicine did not become scientific earlier than was in fact the case. Altogether the book is as charming, lucid, and elementary an exposition of its great theme as can be found in any such small compass.

CHARLES SINGER.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Wisdom, Madness and Folly. By J. Custance. (Pp. 252. 16s.) London: Victor Gollancz. 1951.

Scientific and Learned Societies of Great Britain. A Handbook compiled from official sources. (Pp. 227. 30s.) London: George Allen and Unwin. 1951.

The Child Unborn. By R. J. Harrison, M.A., D.Sc., M.B., B.Chir., F.L.S. (Pp. 226. 15s.) London: Routledge and Kegan Paul. 1951.

How I Cured My Duodenal Ulcer. By J. Parr. (Pp. 160. 8s. 6d.) London: Michael Joseph. 1951.

The History of Capital Punishment. By G. Ryley Scott, F.Ph.S., F.Z.S., F.R.A.I. (Pp. 312. 21s.) London: Torchstream Books. 1950.

Studies in Pathology. Edited by E. S. J. King and others. (Pp. 350. 35s.) London: Cambridge University Press. 1951.

Pediatric Allergy. By R. Chobot, M.D. (Pp. 284. 38s. 6d.) London: McGraw-Hill Book Company. 1951.

Modern Surgery for Nurses. Edited by F. Wilson Harlow, M.B., B.S., F.R.C.S. 2nd ed. (Pp. 799. 25s.) London: William Heinemann. 1951.

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REMUNERATION OF G.P.s

The Special Conference of Representatives of Local Medical Committees on Thursday last week passed as a resolution the recommendation of the G.M.S. Committee that the amount of money to be paid to general practitioners in the Health Service should be decided by arbitration. The recent moves in this matter, brought to a head by the Minister of Health's tactless offer of £2m., with conditions, have been thoroughly discussed in the G.M.S. Committee[1] and by the Annual Representative Meeting,[2] and, too, have been the subject of comment in these columns.[3] The Minister of Health, after previously admitting that there was a *prima facie* case for reviewing the remuneration of general practitioners, said subsequently that any additional money would be limited by the ceiling of £400m. for the Health Service as a whole. When the letter from the Ministry was sent the difference between what was believed to be the cost of the Health Service then and this ceiling was £2m.; but, as we pointed out last week, revised estimates for the Health Service show that the total cost has gone up over £1m. above the figure originally presented to Parliament. It may reasonably be assumed, therefore, that if the Ministry's letter had been written now the amount offered would be slightly less than £1m. This is another illustration of the incredible mess the finances of the N.H.S. have got into—another example of the price we have to pay for what the *Manchester Guardian* has described as "Bevanity." Mr. Marquand is in the unenviable position of having to put ceilings on the rooms of the mansion known as "Bevan's Folly." He has to do this on an expenses allowance that gets less and less as the cost gets more and more; and, too, he is having to do this when his tenancy of this derelict building looks as if it may be coming to an end. Although the profession may sympathize with him in his predicament the temper of last week's conference and, what is more, the hard facts of the situation make an inquiry in the shape of arbitration imperative.

Various calculations have been made at various times about the sum that should be added to the central pool to bring it into relation with the recommendations of the Spens Committee. But what is outstanding is lack of agreement, or, indeed, lack of discussion, with the Ministry on the betterment factor. The Spens Report laid down certain ranges of income for certain proportions of doctors in terms of the 1939 value of money, and stated that these sums would have to be related to the changed value of money and the rise in incomes of other professions. Unbelievable as it may seem, general practitioners three years after the introduction of the Health Service have been given no satisfaction on this point, and they are now driven to request arbitration on, in effect, the betterment factor.

There can be little doubt that an independent tribunal will, on examination of the facts, make an award far in excess of the £2m. offered by Mr. Marquand, and the resulting national bill for the Health Service will thereby exceed the limit of £400m. placed on it by the Chancellor of the Exchequer for the current financial year. It is possible that political apologists may seek to persuade the general public that the doctors are asking for more money at a time of financial embarrassment to the country because of the cost of rearmament. It is possible that the Government itself may find it convenient to appeal to the self-denying patriotism of the medical profession in forgoing temporarily the just payment for its work. The medical profession should be forearmed against such specious pleas and emphasize on all occasions that they are not, as the *Manchester Guardian*[4] put it, "asking for a rise to meet the latest increase in price but to meet the increase over twelve years." Mr. Marquand and his advisers must recall that general practitioners, in particular, entered the Health Service with great reluctance and, indeed, only on the assumption that their terms and conditions of service would be reviewed at the earliest moment after July, 1948. Mr. Marquand, too, must be well aware of the mounting and justifiable discontent of general practitioners with their conditions of work and with the way that they have been fobbed off with one excuse after another, so that, it would seem, the Ministry and the Treasury should avoid having to make an adequate payment for the medical services the Government promised to provide for the country—promised, as it daily becomes more evident, with an improvidence equalled only by the improvi-

1 *British Medical Journal Supplement*, 1951, 1, 242.
2 Ibid., 1951, 1, 262.
3 *British Medical Journal*, 1951, 1, 1372, 1435, 1438.
4 *Manchester Guardian*, July 18, 1951.
5 *The State and the Doctor*, by Sidney and Beatrice Webb. Longmans Green, 1910.

dence with which it entered into the Groundnuts Scheme, and tried to produce eggs in Gambia without knowing whether it could feed the hens that were to lay them. Sooner or later a Government will have to overhaul completely the financing of the Health Service on the basis of restoring a proper sense of responsibility to those who use it. Sidney and Beatrice Webb[5] as long ago as 1910 concluded that unless Parliament and local authorities were able "to devise any convenient machinery for charge and recovery, [they] may slip unawares into free doctoring, without protecting the interests of the present generation of medical men." Seeing that through emphasis on preventive medicine doctors would be able to inculcate in their patients a greater concern with healthy living, the Webbs observed: "The only complaint that is made against the Public Health Service, from the standpoint of those concerned for the maintenance of a sense of individual responsibility, is that this bracing influence on personal conduct is not always combined with a pecuniary charge." Once the Government has met fairly the just claims of general practitioners in the Health Service it will, we believe, be forced to consider, not only on economic grounds but with the aim of inculcating a sense of personal responsibility among the users of the Service, the bracing influence of pecuniary charges for medical benefits.

TREATMENT WITH CORTISONE

It is only just over two years since the antirheumatic effects of cortisone in rheumatoid arthritis were announced, but in that time opinions of its value have fluctuated violently. After being heralded as the "wonder drug," despite the warnings of the workers at the Mayo Clinic, it has lately been described in the U.S.A. as a "glorified aspirin." This apparent drop in prestige has been due to the fact that supplies of cortisone, even in America, have been severely limited; there has therefore been a widespread element of frustration and few centres have been able to undertake a large number of long-term studies. All the more importance therefore attaches to Dr. E. W. Boland's report in this issue, for it is by such work that the value of cortisone will find its right level.

Dr. Boland repeats what Hench and his colleagues have said again and again, that cortisone suppresses rheumatoid arthritis but does not cure it. This fact ought to be universally accepted and with it the necessity for indefinitely prolonged treatment. Two methods of administration are possible: the drug can be given either in courses with intervals between them or in continuous maintenance dosage. Boland has studied the latter and believes that it is the better method. Cortisone is not substitution therapy, for there is no evidence of adrenocortical deficiency, though Boland reports that Dobriner has found some quantitative alterations of steroids in this disease. However, the drug must be given in sufficient quantities to induce a state of hormone excess, so that from a practical point of view the problem is similar to that of giving insulin in diabetes. Four important questions have to be asked about indefinitely prolonged treatment of this kind. First, does the drug continue to work effectively if given for long periods? Secondly, are there harmful side-effects? Thirdly, are there other methods of treatment which will prevent crippling in rheumatoid arthritis? And, fourthly, is long-term treatment feasible from an economic point of view?

The first question is usefully discussed in Boland's paper, for the number of his patients and the length of treatment are sufficient to give significance to his findings. Administration of cortisone had to be stopped in 16 of 76 patients started on prolonged treatment, and study of these cases is important. In half of the 16 it was found that response was not sufficient to warrant the continuation of treatment, in seven there was a hormonal reaction, and in only one did a remission develop during treatment which made continued administration of cortisone superfluous. The severe cases of rheumatoid arthritis obviously present the most difficult problem, for, though in 68% of those so classified an adequate response was obtained, the majority of the patients whose treatment had to be stopped came into this group. It would be interesting to know whether Dr. Boland, in classifying a case as severe, gave greater weight to length of history and amount of permanent joint damage or to evidence of activity, as shown by loss of weight and high sedimentation rate. In the other 60 cases in this series the results of continued therapy were impressive and satisfactory, improvement being maintained in 48 patients. In the moderately severe and mild cases the results were extremely good; maintenance doses were low and side-effects minimal.

The second question, that of the side-effects of cortisone, has caused much speculation about their exact causation, whether endocrine or electrolytic. Side-effects occurred in over one-third of Dr. Boland's patients, being more marked in the severe cases requiring a high dosage. Though treatment had to be stopped in only two cases, dosage modifications had to be

made in many others, with consequent difficulty of control. The two commonest side-effects were excessive gain in weight and rounding of the face. It is encouraging that no serious psychic changes were observed. Dr. Boland emphasizes the importance of denying this drug to patients with a psychotic history and of using a minimal maintenance dose to avoid undue mental stimulation as well as other side-effects. The answer to the question about the harmful effects of prolonged treatment therefore seems to be that with careful supervision and a constant effort to achieve a low maintenance dosage they can be avoided in most cases. This is of course only part of the answer, for the fear has been repeatedly expressed that after prolonged cortisone administration the adrenal atrophy which occurs would be irreversible, a most serious consequence of treatment. Dr. Boland believes that if the drug is withdrawn slowly to avoid the asthenia which develops when treatment is abruptly stopped there is evidence that the adrenal function returned to normal, even after continuous treatment for fourteen months. He is going to report separately on this subject.

The third question, that of alternative methods of preventing crippling deformity in rheumatoid arthritis, will not diminish in interest while cortisone is so difficult to obtain. There are of course other known palliatives, and much has been written, even lately, about the value of gold injections. In France and in this country chrysotherapy was recognized as useful long before it was accepted in the U.S.A.: in conjunction with general and local rest and ancillary methods of physical medicine it can suppress symptoms of moderate severity. It is in the severe cases, however, that the limitations of gold and other methods become apparent.

At present the answer to the fourth question, about the high cost of prolonged treatment with cortisone, is not encouraging. While ox bile, with its limited world supply, remains the only source of the drug, and while manufacture is so laborious and expensive, the difficulties of indefinite treatment are enormous. But there is reason to hope that the world-wide chemical research which is now being carried out will be successful in bringing cortisone or a similar drug within the reach of rheumatic patients at a cost which is not impracticably high. Possibly in the long run the present scarcity may not prove to have been altogether harmful: there is no doubt that over-large doses of cortisone, given under inexpert supervision, can cause great damage to the individual patient and great difficulty to those who have to assess the value of the drug.

BATHING IN RIVERS

Opinions about the pollution of rivers and the remedies required differ greatly with the particular interests of those passing judgment. Widespread condemnation has been the theme of a series of reports, none the less valuable because they have been based upon somewhat superficial surveys, recently published on behalf of the British Field Sports Society. The author of these reports has examined the rivers primarily on their ability to support fish life, which means their ability to support the more delicate animal and vegetable organisms, often microscopic, upon which depend the survival and growth of fish.

Some two years ago the Windsor Borough Council, by the closure of their baths in the River Thames, decided to withdraw their official encouragement to bathing in the river, and more recently there have appeared in *The Times* a number of letters deploring "that Eton has decided to bow to the demon of river pollution and make plans to build a swimming-bath at a cost of £60,000." It seems to be widely believed that these decisions have been necessary because the water of the river has become less pure and the risks associated with bathing in it have consequently increased, but there is no substance in such an opinion. It is true that with increasing populations in its catchment area the River Thames inevitably receives more pollution than formerly; but so large a river has great powers of recuperation, and there is no reason for suspecting that the trust imposed in the Thames Conservancy has been misplaced. While there has inevitably been some slight increase in the mineralized end-products indicating past pollution, in themselves neither harmful to health nor detracting from the amenities of the river, there has been no significant increase in the bacterial indices of pollution.

There is a great, though less vociferous, public who enjoy the beauties of rivers without desiring to fish or bathe in them and who, moreover, depend upon them for that first essential of civilized life—a safe and acceptable supply of pure water for domestic use. If it were possible to serve all these varied interests we would be united in a demand that our rivers should be kept in a state of virgin purity, but things are not so simple as that. Piped water supplies and the amenities they confer require the disposal of great volumes of sewage, and polluting effluents which must frequently be discharged to rivers are inevitable accompaniments of industrial processes upon which national prosperity depends. Processes

are available for bringing these to a state in which they will have no lasting effect upon a river, provided that they are sufficiently diluted with good river water, and the standards which are required for this were laid down many years ago in the recommendations of the Royal Commission on Sewage Disposal. The Commission dealt only with chemical standards which, had they been observed, would have been adequate to conserve the amenities of our rivers and to protect fish. Bacterial standards for effluents discharged to rivers, upon which would depend the safety of river water for bathing and drinking, have never been promulgated, for the good reason that a standard would be of no value if it could not be complied with. It is at least open to doubt whether the effluents discharged to rivers could be brought to a state of bacterial purity without serious consequences to the rivers in other directions.

For drinking-water we rely upon purification processes known to be effective. For bathing in the rivers no such protection can be given. Unfortunately it must be accepted that rivers and, indeed, almost all surface waters in a highly populous country will be bacterially polluted, and it would be idle to hope that they could by any practicable measures be maintained in a state of such purity as to comply with the standards prescribed for artificial swimming-pools in the revised edition of the Ministry of Health's pamphlet, *The Purification of the Water of Swimming Baths*. Bathing in the open air is of more benefit than bathing in enclosed and often overcrowded artificial pools, where, as the Ministry's pamphlet implies, the dangers of air-borne infection may be greater than water-borne. Perhaps the fullest benefits of bathing can be enjoyed only at the seaside. But even the sea is not free from dangerous bacterial pollution, and popular beaches are often contaminated by discharges of sewage. Bacteriology cannot give much help in an assessment of the danger to health of bathing in waters not of the standard of bacterial purity prescribed for and attainable in artificial pools. We know that the enteric fevers and spirochaetal jaundice are the diseases most likely to be contracted through bathing in impure water. We know that the causative organisms of the former and probably also of the latter are accompanied by *Bact. coli*, but we do not know what level of *Bact. coli* content might indicate danger. *Salmonella* types are isolated more often from polluted river waters than formerly, but this is probably due to improved methods of recovery rather than to their more frequent occurrence.

In the absence of such positive evidence as the recovery of specific organisms, a common-sense attitude to the dangers of river bathing must be based upon local topographical studies and epidemiological knowledge. Rivers have great powers of self-purification, and, whereas it might be dangerous to bathe a short distance below a sewage outfall, this risk would rapidly diminish and might be negligible within a mile or so. Risks certainly exist, for cases have recently been reported in which the proof has been sufficiently convincing that children had contracted enteric diseases from bathing in polluted streams, but at only a short distance below a sewage outfall. Some might be tempted from this to believe that all bathing in rivers, and even on many beaches, should be discouraged, but such mishaps are rare. Moreover, disease is not the only danger associated with bathing, and there is no proof that the danger from it is greater than that from other causes. In fact the risk of contracting disease from bathing in rivers may be no greater than the risk of attending crowded indoor places of entertainment or travelling in crowded vehicles. This is not to say that responsible bodies should indiscriminately encourage bathing in polluted waters. Schools have a special responsibility towards their charges, and the only surprise about the decision of Eton is that it has been so long delayed. Nevertheless it would be regrettable if there were to be a widespread closing-down of open-air bathing places because the water did not and could not be made to comply with the standards prescribed for artificial pools, unless it had been shown that the water was specifically polluted or unless there was good reason to believe that there existed some feature which created inherent danger.

EOSINOPHILS AS INDICATORS

The fall in the concentration of circulating eosinophils after injections of A.C.T.H., and after various types of "stress," correlates so well with metabolic changes known to be produced by the adrenocortical hormones that it is often employed as an index of adrenocortical activity, particularly since eosinophil counting is so much simpler than other methods of assessing such activity. But it is as yet uncertain that it is always reliable by itself. For instance, large doses of heparin appear to interfere and produce eosinophilia in spite of injections of A.C.T.H., cortisone, and insulin[1]; the theoretical implications of this finding are obscure. A second kind of complication is an initial eosinopenia before A.C.T.H. therapy is begun, in diseases which include bone marrow involvement such as generalized lupus erythematosus; in such a case A.C.T.H. may actually produce a rise in circulating eosinophils due to improvement in bone marrow function. Sevitt,[2] however, on the basis of eosinophil changes alone, postulated that 35 patients he studied had increased adrenocortical activity for one to five days following burns; the duration of eosinopenia

was related to the percentage of body area burned, and cessation of eosinopenia before the expected day he thought might therefore indicate adrenocortical failure and the need for replacement therapy. But five patients died with eosinopenia, which suggests that factors other than adrenocortical activity determined the ability to survive. The eosinopenia he observed is qualitatively similar to that noted by Roche and his colleagues[3] for one to two days after major surgical operations, and its greater duration may be an expression of continuing stress in the burned patients.

Renold and his co-workers[4] at Harvard have recently reported that the average eosinophil count in the boat-race crew at the beginning of training was 123 per c.mm. The count fell after each trial row, and immediately before the race with Yale it was 64. Four hours after the race it had fallen to 3. If this is in fact an indication of an increase in circulatory adrenal oxysteroids, the authors consider that emotional factors are as much concerned in it as muscular. The reason for adrenocortical activity after stress is presumably increased A.C.T.H. production by the anterior pituitary. Nervous stimulation of the dog hypothalamus[5] causes a decrease in eosinophils, and injections of adrenaline have been shown by Recant, Thorn, and their colleagues[6] to have the same effect in man, it is believed by pituitary stimulation. They conclude that if 0.3 mg. subcutaneous adrenaline produces a 50% fall in circulating eosinophils deficiencies of adrenocortical function and of pituitary A.C.T.H. are unlikely. Such a test, if reliable, would be of great value in distinguishing between primary adrenocortical deficiencies and those secondary to diminished pituitary A.C.T.H. For instance, Jailer, Wong, and Engle[7] found that A.C.T.H. produced eosinopenia in both full-term and premature infants as early as the second or third day of life. Adrenaline eosinopenia was found in the majority of full-term infants on the first or second day, but premature babies failed to respond until the ninth day. The authors' interpretation of this is that premature infants have adequate adrenal cortical tissue but deficient pituitary A.C.T.H., and they point out that this correlates with the poor response of premature infants to general stresses.

There are, however, objections to the view that eosinopenia following injected adrenaline is a valid test. It is known that adrenaline may stimulate the adrenal cortex in the absence of the pituitary,[8] and Recant and co-workers deliberately selected the comparatively low dose of 0.3 mg. adrenaline in order to avoid this apparently direct effect, which they also had observed. Many normals fail to produce a 50% decrease in eosinophils after doses of this order,[9] [10] so that a negative response does not necessarily indicate deficiencies of the pituitary-adrenocortical system. In addition, eosinopenia due to adrenaline may not be accompanied by the dramatic metabolic changes which follow A.C.T.H. administration.[11-13] This occasional dissociation between the effects of adrenaline on eosinophils and on metabolism indicates that adrenaline may conceivably affect the eosinophil count through some mechanism other than increase in activity of the pituitary-adrenocortical system. In the light of present experience, therefore, results of adrenaline tests should be viewed with caution until further investigations throw light on their validity.

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2 Ibid., 1951, **1**, 976.
3 *New Engl. J. Med.*, 1950, **242**, 307.
4 Ibid., 1951, **244**, 754.
5 Hume, D. M., and Wittenstein, G. J., *Proc. First Clinical ACTH Conference*, 1950, p. 134. Blakiston, Philadelphia.
6 *J. clin. Endocrinol.*, 1950, **10**, 187.
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8 Vogt, M., *J. Physiol., Lond.*, 1944, **103**, 317.
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ANALGESICS AND INTESTINAL MOTILITY

The action of morphine on intestinal motility is a subject of practical importance about which there has been for some time a difference of opinion. After an abdominal operation there is always the need to relieve pain, and always the possibility, remote though it may be, of intestinal stasis. While morphine is the most effective analgesic, some consider that it contributes to stasis, as its well-known constipating action would suggest; while others point to evidence that morphine has a stimulant action on the gut, from which they conclude that under its influence stasis is less likely to occur. The evidence that morphine delays intestinal propulsion has come in the main from radiological observation and by investigating the passage of fluid contents through the alimentary canal of various animals, including man. The results which indicate the opposite conclusion have come from the insertion of a solid bolus or an inflated balloon into a Thiry-Vella loop or a fistula of the colon.

Vaughan Williams and Streeten[1] appear to have resolved this conflict by experiments on dogs. After cutting out a loop of intestine, they first reconstituted the main canal by a side-to-side anastomosis and then brought the ends of the loop to the body wall and implanted cannulae within them. The passage of fluid through this loop was studied, and, by having the outflow at a higher level than the inflow, the authors were able to measure the work done per minute in propelling the fluid. The injection of morphine was found to arrest the propulsion for a certain length of time, and a measure of the inhibitory effect of a given dose was obtained. The authors also examined the analgesics pethidine and the recently introduced amidone (" physeptone "). Both of these, like morphine, inhibit propulsion, but much less than morphine in doses having the same analgesic action. Whereas morphine ¼ gr. (15 mg.) would abolish intestinal propulsion in a man of 70 kg. for one hour or more, the same dose of amidone would be only just sufficient to cause a detectable inhibition, and pethidine in doses as high as 200 mg. would be well below the threshold for inhibition of propulsive activity. The method used by Vaughan Williams and Streeten has enabled them to demonstrate that the effect of morphine is not to cause a flaccid paralysis of the gut, but rather a spasm of the

1 *Brit. J. Pharmacol.*, 1950, **5**, 584.

musculature, as a result of which the contained fluid is expelled and the entry of more fluid is blocked.

In experiments relying on the insertion of balloons into the gut, the spasm of the muscle caused by morphine has naturally increased the pressure recorded in the balloons. This has given rise to the erroneous idea that morphine may stimulate propulsive movements, whereas in fact the observation is not inconsistent with the opposite view. If a loop of intestine develops a prolonged contracture it is impossible for co-ordinated propulsive movements to occur, even though the capacity for work by the muscle itself may be greater in response to stretching by balloons or by a bolus. Thus Vaughan Williams and Streeten show that, though the different kinds of evidence obtained by them and by earlier workers have given rise to conflicting interpretations, the facts can readily be harmonized. Their work has been done with evident care, and the results appear conclusive on the point at issue.

SWEET AND DANGEROUS

In the past the more unpleasant the medicine the more effective it was supposed to be. To-day the pendulum has swung so far in the opposite direction as to threaten to introduce a complication which may not be without risks to life. There is scarcely a pharmaceutical house in this country or the United States which is not trying to produce attractively flavoured and coloured medicaments. No one would deny that medicines, particularly for children, should be as pleasant as possible, but the danger lies in the fact that it is the potent chemotherapeutic and pharmacological preparations which are being made up in this way, and with these preparations the margin of safety between the therapeutic and the toxic dose, particularly in the case of infants and children, is relatively small. There are probably few practitioners who realize the variety of pleasantly flavoured preparations now available. Even in this country there are at least 10 different sulphonamide suspensions, including practically all the members of this group except sulphanilamide and sulphapyridine. Four of the antihistaminics are available as elixirs, and there are elixirs or syrups containing codeine, phenobarbitone, amidone, myanesin, pentamethonium, and stilboestrol. A cursory glance through the list of sugar-coated tablets sufficiently like sweets to tempt young children shows the presence of six of the antihistaminics, combinations of barbiturate and oestrogens, dextro-amphetamine, and one of the newer antibiotics. The United States, of course, leaves us far behind in numbers and variety.

It is clear that the practitioner should seriously consider the three main risks involved. A careless mother may give an overdose; an enterprising child may discover a bottle of pleasantly flavoured liquid and swallow the lot; and the doctor, on whom the final responsibility falls morally, if not necessarily legally, may not emphasize sufficiently strongly to the mother or nurse that the prescribed dose must not be exceeded under any circumstances. That the dangers involved are not hypothetical has already been proved by the fatalities and near-fatalities recorded from the consumption of excessive amounts of highly coloured and flavoured iron tablets and sedative elixir. Cases of sulphonamide anuria in a well-known children's hospital occurred when excess of an elegant sulphonamide suspension was given. The only way to prevent these accidents is for doctors to prescribe such preparations only when they are satisfied that they will be given under careful supervision, whether in home or hospital, for the margin of safety is small. If there are any doubts whatsoever a plain tablet or mixture only should be ordered. Pharmaceutical firms should give serious consideration to their responsibility when they advertise pleasantly flavoured medicaments to the public. Even aspirin has its risks when attractively coloured and flavoured.

HOSPITAL MORBIDITY STATISTICS

Although national statistics of mortality have been published since 1841 it is only recently that an attempt has been made to assess the relative importance of the many non-fatal illnesses. Such a study must clearly be of great interest to those concerned with the administration of the health services, but the other uses to which it can be put have not always been immediately obvious to clinicians. A hundred years ago Farr, who aimed at obtaining a return of the sicknesses of the civil population as complete as that procured from the Army, believed that morbidity statistics would be an invaluable contribution to therapeutics and would enable clinicians to determine the duration and fatality of all forms of disease under different methods of treatment and among different sections of the people. Such a belief cannot now be substantiated, but there can be no doubt of the extent to which the understanding of the nature of disease processes is increased by a knowledge of the relative incidences with which they occur in men and women at different ages and among different social classes and occupational groups. Illnesses treated in hospital form a highly selected fraction of all illnesses, but it is natural that their study should be an intermediate step between the study of mortality statistics and the total analysis of illness desired by Farr. The fourth report[1] in the series of "Studies on Medical and Population Subjects" issued by the General Register Office is a preliminary study of in-patient discharges from a number of hospitals in the first six months of 1949. That the report is a preliminary one is stressed throughout; the hospitals co-operating were known not to be representative of all the hospitals; the returns were incomplete, and several problems—such as the classification of repeat admissions for the same illness and multiple causes of illness—have not yet been solved. The preliminary tables show, however, the kind of information which the systematic reporting of in-patient discharges can provide and give the potential users of such statistics an opportunity of constructive criticism. Despite its limitations the information in this report—if used with discretion—will be of appreciable help to research workers.

[1] Mackay, D., *Hospital Morbidity Statistics*, Studies on Medical and Population Subjects, No. 4, 1951, H.M.S.O., London.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

BLOOD GROUPS AND DISPUTED PATERNITY

BY

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The paternity of a child may be disputed either when the child is born in wedlock and the husband denies paternity or when the child is born out of wedlock and the man named as the father denies paternity. The first set of circumstances may lead to divorce proceedings, while the second results in an action by the woman to obtain a court affiliation order against the man in respect of her child. In actions of the latter sort the sympathy of the court is usually with the woman, who presents a rather pathetic figure, and, though the Bastardy Laws Amendment Act, 1872, requires that the woman's story be corroborated "in some material particular," the degree of corroboration demanded by the average bench of magistrates is not exacting. Consequently gross injustice might be done to a man wrongfully accused by a mendacious woman, and he would be left almost defenceless. The attitude of some courts is shown by the evidence given by a well-known Metropolitan Police magistrate before a Parliamentary Committee considering the Bastardy (Blood Tests) Bill, 1938. He said that he would hold as the father of the child any man who had had intercourse with the woman about the probable time of conception. His evidence was based on the assumption that "the man who may be the father must pay," whether he is in fact the father or not.

This state of affairs is being rectified in many parts of the world as the value and reliability of blood grouping in determining blood relationship become more widely appreciated. In 1924 blood grouping in affiliation proceedings was introduced into the German courts, and it was estimated that by 1929 the tests had been applied in Germany in more than 5,000 cases. Other countries which followed suit include Austria, Denmark, Norway, Lithuania, Czechoslovakia, Holland, Sweden, Japan, Russia, Italy, Belgium, and the United States of America. In many jurisdictions not only is the result of the test accepted in evidence but the courts have the power to compel the parties involved to submit to a blood examination. In Great Britain there is, as yet, no statutory power of compulsion, as the Bastardy (Blood Tests) Bill had to be shelved to make way for more urgent legislation just before the outbreak of war in 1939.

History

The first observations of the agglutination of human red cells by serum belonging to the same species were made by Landsteiner in 1900. The discovery that the blood groups were inherited characteristics increased their importance. In 1910 von Dungern and Hirszfeld established the Mendelian inheritance of the groups, but it was not until 1924 that the exact manner of their inheritance was worked out by Bernstein. In 1926 Landsteiner and Levine discovered the MN system and the P system. In 1939 and 1940 Levine and Stetson and Landsteiner and Wiener discovered the Rh groups. Within the last six or seven years five more systems have been discovered: these are the Lutheran, Kell, Lewis, Duffy, and Kidd.

Genetics

Before a characteristic can be used in the study of inheritance it must be shown that it is free from the influence of age, diet, disease, or climate. The blood groups fulfil these requirements. Further, they remain constant from birth till death.

The characters of the body, in the widest sense, are controlled by hereditary factors called genes, which are present in every cell. They are passed from parents to offspring in the gametes. The genes exist in pairs called "allelomorphs," whose members are derived one from each parent. The two genes comprising an allelomorphic pair may be either similar ("homozygous") or dissimilar ("heterozygous"), and the persons possessing such allelomorphs are called "homozygotes" or "heterozygotes." When two genes are brought together in a cell they retain their identity and do not fuse.

In man each somatic cell carries 24 pairs of chromosomes in which the genes are located, but during meiosis the number is reduced by half. Each gamete is really only half a cell from the genetic point of view, and fertilization is an additive process during which the number of chromosomes is restored to 24 pairs. This theory of heredity was enunciated by Mendel (1822–84). Thus, if a person belongs to the blood group AB, one germ cell will carry the A gene and its fellow the B gene; therefore at fertilization the new being will receive either an A gene or a B gene from that parent, but not both.

In an individual, homozygous with regard to a particular pair of genes, the characteristic attributable to these genes will show strongly. If in a heterozygote the same characteristic manifests itself equally as strongly as in the homozygote, then that characteristic is said to be "dominant" and the alternative characteristic, which is obscure in the heterozygote, is called a "recessive." This is Mendel's first law. Dominants therefore may be of two genetic types—homozygotes or heterozygotes—while recessives can only be homozygotes. If two different allelomorphic genes both express themselves and can be detected together then they are co-dominants—for example, M and N. A true recessive characteristic is not detectable in the presence of the dominant characteristic, other than by breeding experiments or family studies.

Mendel's second law is to the effect that when two or more pairs of genes segregate (separate) simultaneously the distribution of any one of them is independent of the distribution of the others. But in man, although there are probably many thousands of allelomorphs (pairs of genes) in each cell, there are only 24 pairs of chromosomes. Therefore the individual pairs of human genes cannot assort entirely independently: as they travel in the same vehicle (the chromosome) they may consequently be expected to reach the same destination. This tendency for pairs of allelomorphs to assort together because they are carried in the same

pair of chromosomes is called "linkage." All the genes in a particular pair of chromosomes are linked together, but no genetic linkage has yet been detected between any of the eight blood group systems.

The position of a gene upon a chromosome is called its "locus." The closer the loci, the closer the linkage between the genes, and those genes with loci exactly opposite one another in a pair of chromosomes are, of course, allelomorphs. It is sometimes possible for a particular gene to exist in more than two phases, so giving rise to a series of "multiple allelomorphs," but not more than two members of such a series can coexist in the same individual.

The type of an organism judged by its characters is designated its "phenotype," while its "genotype" is its genetic constitution. Thus, to say that a person's blood belongs to group A is to give its phenotype; but two group A bloods may be genetically different—that is, either A/O or A/A. Therefore, a *phenotypical* description of some character is incomplete from the genetic point of view. The blood groups are controlled genetically by a system of multiple allelomorphs. For example, group O is due to the operation of a pair of allelomorphic genes O/O. Groups A and B are each produced by a different gene substitution (A or B). Both A and B genes are co-dominant with the gene O. It will be evident from the above that, from the point of view of blood grouping, the results of any mating can be predicted within certain limits once the mode of inheritance of the blood factor in question is established with certainty.

The Blood Group Systems

It is now known that there are at least eight systems identifiable in the blood of man—that is, ABO, MNS, P, Lewis, Rh, Lutheran, Kell, and Duffy. The mode of inheritance of some of these factors has now been established beyond reasonable doubt, one might almost say with absolute certainty, and only these groups can be safely used in excluding paternity. As more and more family studies accumulate, doubtless the mode of inheritance of the others will be elucidated, and they also will be utilized.

ABO Groups

In 1900 Landsteiner, who discovered this initial system, showed that, according to whether the red cells contain one or other, both, or neither of the two antigens A and B, the blood of human beings could be classified into four groups—that is, four phenotypes—A, B, AB, or O. He also demonstrated that the serum of an individual does not contain the antibody for an antigen present in his own red cells. In 1911 the subgroups A_1, A_2, A_1B, and A_2B were described. Next was reported the occurrence of individuals of group A whose blood gave only feeble reactions even with the most potent anti-A sera; this was attributed to a third sort of A agglutinogen named A_3. The existence of the agglutinogen A_3 gives rise to two additional subgroups in group A—namely, A_3 and A_3B—but these subgroups are extremely rare. Recently it has been found that on testing unknown cells with anti-A, anti-B, and serum from an O person (anti-A + anti-B) the O serum on rare occasions agglutinated cells which did not react with anti-A or anti-B or with mixtures of both. This reaction was due to the presence of the agglutinogen A_4. Such bloods would have been mistakenly regarded as O blood if the O serum had not been used. This subgroup is also very rare.

Inheritance.—Bernstein's theory of the mode of inheritance of the ABO antigens is now accepted as the correct one. It postulates three allelic genes—A, B, and O. Under this theory there is only one locus for the genes determining the blood groups in a single pair of chromosomes, at which locus any one of three genes may be situated. As each germ cell contains only one of the three genes A, B, or O from combinations of the three possible kinds of sperms with one of the three possible kinds of ova, six different genotypes result. Furthermore, the genotypes corresponding to each of the four blood groups are:

Phenotype	Genotype	
	Homozygous	Heterozygous
AB	—	A/B
A	A/A	A/O
B	B/B	B/O
O	O/O	—

The agglutinogens A and B cannot appear in the blood of a child unless present in the blood of one or both parents. It follows that if either parent is A/B the child cannot possibly be of the genotype O/O. Similarly, if either parent is genotype O/O, the child cannot be A/B. According to Bernstein's theory group O blood is not just A – B – blood, and therefore persons of genotype O/O would be expected to possess the agglutinogen O in their red cells; the discovery in 1948 of the existence of sera which selectively agglutinate group O blood supports the theory. With regard to the heredity of the subgroups of A it is postulated that instead of the three allelic genes A, B, and O there exist four allelic genes A_1, A_2, B, and O. This extension of Bernstein's theory is supported by many family studies.

Source of Antisera.—As group A blood serum naturally has the antibody α (anti-B), and group B blood serum naturally contains the antibody β (anti-A), by suitable selection sera of a sufficiently high titre for testing purposes can be obtained from routine blood donors. All anti-A sera (from group B donors) contain two anti-A antibodies α and α_1. Anti-A agglutinates the cells of all the subgroups A_1, A_2, A_1B, and A_2B, while α_1 (anti-A_1) agglutinates A_1 and A_1B cells only. The simplest method of subgrouping A and AB blood is with the aid of so-called "absorbed B serum." This is based on the fact that all group B sera contain two sorts of agglutinins—namely, the common anti-A agglutinin, which acts on both A_1 and A_2 cells, and anti-A_1, which reacts only with A_1 cells. When the common anti-A agglutinin is removed from such sera, only that isoagglutinin remains which reacts with A_1 cells, so that in tests with such a reagent, if agglutination occurs the blood belongs to subgroup A_1 (A_1B), and if no agglutination occurs the subgroup is A_2 (A_2B). The anti-A_1 serum is prepared by absorbing selected B serum with A_2 cells. This removes the anti-A which acts on A_1 and A_2 cells, leaving the anti-A_1 in pure form.

MNS Groups

In 1927 Landsteiner and Levine showed that the M and N factors in the erythrocytes were independent of the ABO system. There are three types of blood—M, N, and MN—and no blood lacking one or other has ever been found. There are two allelomorphic genes—M and N—either of which determines, in single or double dose, the presence of the equivalent antigen in the red cells. An additional factor N_2 has been described, but it is very rare.

The pleasing simplicity of the MN system was complicated by the discovery in 1947 of a new antibody associated with M and N. This was called anti-S, and its association with the MN system was proved

statistically, though no association between S and the other systems could be found. It is possible that S is a separate gene having an allelomorph s.

Inheritance.—The agglutinogens M and N cannot appear in the blood of a child unless present in one or both parents, and M type parents cannot produce an N child, and vice versa. Not a single proved exception to this theory has been encountered in studies on a total of more than 15,000 children. Anti-S is a relatively recent discovery, and consequently extensive family studies have not yet been possible. One would therefore be on unsure ground in excluding paternity on the strength of the factor S alone. However, in a study of 123 English families none of the children was an exception to the theory of inheritance. Statistical analysis further bears this out.

Source of Antisera.—Anti-M and anti-N sera occur naturally in human blood, but not often enough or of sufficient potency to provide for routine testing. Normally these sera are prepared by the injection of OM and ON cells into rabbits. The rabbit serum is absorbed with cells from an A_1N person or an A_1M person respectively, to get rid of species specific antibodies and of the naturally occurring anti-A_1 which is sometimes present in rabbit blood. The correct preparation of these sera is technically difficult and requires much experience. Anti-S has been found only in human serum. It may be of natural or immune origin and is not in plentiful supply.

P Groups

In 1927 Landsteiner and Levine discovered that, when the sera of certain rabbits which had been immunized with human red cells had been absorbed to eliminate the species agglutinins, the rabbit serum could agglutinate some samples of blood and not others. The distinction could not be explained on the basis of the ABO or MN systems, and the two types of blood were called P+ and P−. These workers later found anti-P in a human being. The P factor is independent serologically of all the other known blood groups.

Inheritance.—P is inherited as a simple Mendelian dominant by a pair of genes P and p. Therefore a P+ child cannot result from the mating of P− parents.

Source of Antiserum.—This was originally obtained by immunizing rabbits, but it occurs naturally in human serum. It tends to vary in strength, and it may be difficult to distinguish between a weak P+ and a P−.

Rh Groups

In 1940 Landsteiner and Wiener, having immunized rabbits and guinea-pigs with the blood of the Rhesus monkey, found that the resulting antibodies in the rabbit and guinea-pig serum agglutinated not only the monkey red cells but also the erythrocytes of 85% of the sample of the white people of New York City tested. The former were classed Rh+ and the remaining 15% Rh−. The next discovery was that apparently the same antibody (anti-Rh) as that made by the rabbit against the monkey cells was present in the serum of persons who had had transfusion reactions following transfusion of blood of the correct ABO group. It was then shown that incompatibility of these groups between mother and child was the cause of erythroblastosis foetalis, and it became evident that the stimulation of blood group antibodies in the circulation of a person lacking the equivalent antigen could occur in at least two ways, either by transfusion of blood containing the antigen they lack or by sensitization of a pregnant woman by a foetus possessing an antigen (inherited from the father) which she does not have. At first people were simply divided into Rh+ and Rh−, but it was ultimately shown that this system was more complex.

Five antigens have been discovered—namely, C, c, E, e, and D (named by Wiener rh′, hr′, rh″, hr″, and Rh_0). According to Fisher's theory there are six Rh antigens in three pairs, Cc, Dd, and Ee, and each of these antigens can in certain circumstances stimulate the production of its equivalent antibody, the relationship between the members of these pairs being one of genetic allelomorphism (see above). However, the antigen d has never, up to date, been conclusively demonstrated and Wiener doubts if it ever will. Weiner and Fisher disagree also about whether the three allelomorphic sites of Fisher are in one gene or in three genes, but the recent finding of a blood with the Rh antigenic formula —D—/—D— (no C, c, E, or e being present) seems to settle the dispute in favour of Fisher. The three genes C or c, D or d, E or e are carried in the same chromosome. This is proved because, if a person inherits say cde from one parent and CDe from the other he hands on to his children either cde or CDe. If the genes were in different pairs of chromosomes he would as often pass on Cde or cDe or CDe or cde. In addition to the genes being on the same chromosome, they are closely, or perhaps absolutely, linked.

A third antigen and gene allelomorphic with C and c is known; it is called C^w. Several examples of the specific antiserum anti-C^w have been found. The seven genes, C, c, C^w, D, d, E, e, can be combined in a chromosome in twelve different ways and therefore 78 different Rh genotypes are possible. As anti-d serum is rare or non-existent, and in any case is certainly not generally available, using the remaining six antisera, 28 distinct Rh types can be recognized.

Inheritance.—In the case of the Ee and Cc antigens, the agreement between the observed and the expected distribution of the children, based on Mendelian inheritance, is very close. In the case of Dd, when the antigen D is absent from the blood of both parents, it is not found in the children's blood. It is clear that a child cannot have an antigen D, d, C, c, E, e, if both its parents lack it. Further, the antigens are handed on in threes—for example, if a man inherits CDe from his mother and cdE from his father, then he, in turn, may transmit to his offspring either his three maternal antigens CDe or his paternal antigens cdE. If the exact genotype of an individual cannot be determined with certainty by the use of anti-D, anti-E, anti-e, anti-C, and anti-c, then a family study may make it possible to deduce what it must be. When the genotype is not certain, but alternative or probable, the alternatives are allowed for in assessing the children possible from various matings. These alternatives do not in any way invalidate the use of the Rh groups in cases of disputed paternity.

Source of Antisera.—The main source of Rh antibodies is the serum of human beings who have been immunized by transfusion or pregnancy. Intentional immunization of volunteers is another source.

Other Blood Group Systems

Mention must briefly be made of other blood group systems which, though they cannot yet be safely used in excluding paternity because of lack of sufficient data regarding their mode of inheritance, will undoubtedly be established in this field of serology in the near future.

The Lutheran antibody was found by Callander and Race in 1946. It was of immune origin and appeared after a

transfusion of blood containing the provocative antigen. It has been decided to call the antibody anti-Lu^a; the phenotypes Lu(a+) and Lu(a−); the genes and antigens Lu^a and Lu^b. At present, the gene Lu^b can be recognized only as an absence of Lu^a, as an anti-Lu^b serum has not yet been found. Investigations to date appear to show that the antigen Lu^a is inherited as a Mendelian dominant.

The Kell blood groups (K) were discovered by Coombs, Mourant, and Race in 1946. Up to 1950, 16 examples of this antibody had been recognized. The corresponding antigen k was found in 1949.

The Lewis groups were discovered in 1946 by Mourant. The antibody anti-Lewis was considered to be of spontaneous origin. The antigen is independent of all other known blood groups. There are two agglutinogens in this system, Le^a and Le^b. The genotypes are Le^a Le^a, Le^a Le^b, or Le^b Le^b. If only one antiserum, anti-Le^a, is used, the phenotypes which it defines are called Le(a+) and Le(a−). If both anti-Le^a and anti-Le^b have been used, the phenotypes are called Le(a+b−), Le(a−b+), or Le(a−b−). The Lewis factor is inherited as a Mendelian recessive.

The Duffy blood group system was discovered by Cutbush, Mollison, and Parkin in 1950. The antigen was shown to be inherited by means of a gene expressing itself in single or double dose, and the notation adopted was Fy^a and Fy^b for the genes, giving rise to genotypes Fy^a Fy^a, Fy^a Fy^b, and Fy^b Fy^b. Nothing is known with certainty about the mode of inheritance of the Duffy genes.

A serum that identifies another new blood group antigen was obtained from the parturient mother of a baby with erythroblastosis foetalis by Allen, Diamond, and Niedziela in 1951. This was called the Kidd antigen and it is independent of the other systems. It is present in the blood of about 77% of Americans. The inheritance of this group is now under investigation. This new antigen has been called Jk^a. The phenotypes are Jk^a+ and Jk^a−, with genotypes Jk^a Jk^a, Jk^a Jk^b, or Jk^b Jk^b.

Blood-grouping Technique

There are many variations in technique, each worker adhering to that which he finds most satisfactory. Only one will be briefly described.

It is most important that glassware, syringes, etc., should be clean, quite dry, and free from all traces of alcohol, ether, or other antiseptics. Contaminants may cause haemolysis and render the sample unfit for testing. If the parties can visit the laboratory personally, then a few drops of blood may be taken from the finger or lobe of the ear and suspended in several millilitres of normal saline in a test-tube. The sample may be used direct, or it may be washed once by centrifuging, pouring off the supernatant fluid, and resuspending the cells in fresh saline solution. It is preferable, however, to test both the cells and the serum, and therefore it is better to take a few millilitres of blood by venepuncture, place the blood in a test-tube, and allow it to clot. It is then rimmed and centrifuged, when some of the serum can be pipetted off into a separate tube. Free cells in the serum round the clot can be drawn off and suspended in saline. This is centrifuged, the supernatant fluid is removed, and the cells are resuspended in saline to make a 2% suspension. The cells are now ready for use. If the blood is to be sent from a distance, experience shows that it travels best as clotted blood, and on arrival it can be dealt with as described above. It is necessary to have available a supply of reliable antisera—namely, anti-A, anti-A_1, anti-B, O, anti-M, anti-N, anti-S, anti-P, anti-D, anti-C, anti-c, anti-E, anti-e, and anti-C^w. Also, to test the unknown sera, a 2% saline suspension of known A, B, and O cells must be available.

The tests are carried out in round-bottomed tubes of 6 mm. internal diameter, and the tubes are arranged in a series of Ministry of Agriculture and Fisheries blocks —6.4 by 3 by 1.5 in. (16.25 by 7.6 by 3.8 cm.)—with apertures for the tubes in five rows of ten. Each block bears a permanent number on one face, and that face is always the front of the block. The number serves for identification and orientation. Before testing begins, a plan of the tests is drawn up on a series of diced diagrams corresponding to the blocks in use. Each diagram is numbered to correspond to a block, and the sera and cells to be placed in each tube are indicated on the diagram. It is thus unnecessary to label the tubes in any way.

Block 244

	Cells				Serum					
	Miss S	Baby S	Mr. Y		Controls			Miss S	Baby S	Mr. Y
Anti-A ..					A_2	O	A cells			
Anti-A_1 ..					A_1	A_2	B cells			
Anti-B ..					B	O	O cells			
O serum (anti-AB) ..					A_2	O				

Arrangement of tubes in block.

One drop of the appropriate antiserum and one drop of cell suspension are pipetted into each tube. The tubes are then allowed to stand at the appropriate temperature for the reaction for from one and a half to two hours. The reactions from the ABO groups, the MNS groups, and the P group take place best at room temperature (18–20° C.), whilst the tests for the Rh factors are best done at 37° C. A drop of the material in each tube is then pipetted off, spread gently on a microscope slide, and the reading made microscopically. The results are entered on the prepared charts.

It is imperative that each antiserum should be controlled to ensure specificity and potency by using both positive and negative controls. The positive control must be a weak-reacting cell so that if this cell is agglutinated by the antiserum used under test conditions the test cell will be agglutinated if it contains the antigen. The negative control cells should be strong reactors for the antibodies which should be absent from the antiserum. This controls the specificity of the serum. In the case of the ABO groups, as both cells and serum are tested, it is unnecessary to employ more than one set of antisera. However, in the case of the other groups it is advisable to use two or more different antisera as an additional check. In the case of very rare antisera this may not be possible. The various controls used are shown in the Table.

Antiserum	Controls		
	Positive	Negative	Absorption
Anti-A	A_2	O	—
Anti-A_1	A_1	A_2	—
Anti-B	B	O	—
O	A_2	O	—
Anti-M	MN	N	—
Anti-N	MN	M	—
Anti-S	S+	S−	A_2B S−
Anti-P	P+	P−	A_2B P−
Anti-D	CDe/cde	Cde/Cde	A_2B cde/cde
Anti C	CDe/cde	cDE/cDE	A_2B cde/cde
Anti-E	CDe/cDE	CDe/CDe	A_2B.cde/cde
Anti-c	CDe/cde	Cde/Cde	A_2B.CDe CDe
Anti-e	cde/cde	cDE/cDE	A_2B.cDE/cdE
Anti-C^w	C^wDe/cde	CDe/CDe	A_2B.CDe/CDe

It should be pointed out that the Rh factor controls are possible controls, not the only ones. Serum which has had its anti-A and anti-B agglutinins removed by absorption, as in the case of anti-P, anti-S, and the anti-sera for the Rh factors, is apt during storage to regain its agglutinin content. This might lead to false positives amongst A, B, or AB cells. A further control in these cases is necessary to allow for this possibility. The absorption controls are A or B or AB cells (according to the agglutinins absorbed) lacking the antigen to the antibody in the test serum—for example, AB.cde/cde for controlling absorbed anti-D serum. When the reactions are being read the controls must be examined before the actual tests. With the completed charts it is possible to determine whether the child in question could result from the mating of the parents.

Chances of Exclusion

The putative father in a case of disputed paternity naturally wants to know what his chances of exclusion are if he is innocent and submits to the tests. The answer depends on which blood groups are examined. With the ABO groups alone a falsely accused man has one chance in six of establishing his innocence. With the subgroups A_1 and A_2 his chance is increased by only a further 2%. With the ABO and MN groups together the chances of excluding paternity are raised to 30%. When the ABO, MN, and Rh factors are taken into account the chance of exclusion of a falsely accused man rises to 55%. In actual practice that percentage of exclusion is never achieved, as many of the men accused are actually the natural fathers of the children in question. It must be remembered that paternity can never be absolutely proved by blood grouping. *If the groups of the parties are such that the putative father could be the father of the child in question, the tests are inconclusive and should not be regarded as incriminating the man.* He, or any other man of the same blood type, might be the father. If, however, the child has in its blood an antigen which could not possibly have been inherited from either the mother or the putative father, then paternity can be definitely excluded.

Age of Development of the Blood Groups

The antigens ABO can be demonstrated in the foetus at 37 days and the sensitivity of the cells increases through antenatal and postnatal life up to the age of 20 years. The agglutinins are usually not developed at birth but rapidly increase in titre thereafter. The M and N factors are well developed in the newborn, and the same applies to the S antigen. That the Rh factors develop during intrauterine life is proved conclusively by the fact that an Rh-negative mother may develop antibodies to an antigen which is present in the foetus and which she does not possess. It is therefore safe to use the blood groups for medico-legal purposes when a child is in the early months of post-natal life.

Identification

In all medico-legal work accurate identification is vital, and attempts at impersonation must be prevented. If the parties attend at the laboratory together to have the samples taken, then they can identify each other. Usually they prefer not to do this, in which event they should produce some identification document such as a passport or a National Registration identity card, and leave a signature. Wiener makes the mother and the putative father sign the report form, takes their thumbprints, and takes a footprint from the baby. If the parties attend with a witness, then the name and address of that person should be noted.

If the blood is taken by someone other than the serologist for transmission by registered post, then each party should sign the label on the container in which the blood is put and complete a certificate, to be sent with the blood, certifying that the blood in the container bearing his or her signature is his or her blood. As an additional precaution the signed label may be used as a seal for the stopper, so that if the signed label arrives intact the possibility of the sample having been tampered with in transit is eliminated.

Presentation of Results

The results are usually presented in the form of a certificate giving the blood groups of the parties concerned in the case. There then follows an explanation of the results, stating whether the putative father could or could not be the natural father of the child in question. In the former event it is pointed out that the test is inconclusive and should not be considered as incriminating the man.

Nova et Vetera

THE TRAINING AND PRACTICE OF A LONDON PATHOLOGIST, 1637-46

BY

J. J. KEEVIL, D.S.O., M.D., F.S.A.

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Dr. Robert Wright was an exceptionally brilliant man, but in his lack of inherited wealth, dependence on patronage, and the brevity of his academic course he was the prototype of the London physician of his day. The qualifications M.D.Cantab., M.D.Leyden, F.R.C.P. are now obtained with such difficulty that it is hard to realize that in Wright's case they rested on no more than twelve days passed in a university. This indicates that the statutes of the English universities, requiring fourteen years of medical study before proceeding to the M.D., must be viewed with reservations.

At the Royal College of Physicians there are several biographical manuscripts, written in Latin, which are a guide to the actual procedure. The life of Robert Wright is recorded in one of these. He was born in London about 1600 and was left an orphan, without money, before he could be apprenticed to any calling. Presumably about 1615 "he offered his services to Dr. Robert Fludd . . . in order to be educated." In Fludd's house he worked "as a reader in the evenings and a scrivener in the small hours; in the daytime he sometimes did the work of an apothecary, and in his few hours of leisure he tirelessly followed the doctor's example and diligently read philosophy." Fludd was a Rosicrucian philosopher, and in spite of his D.M.Oxon. his progress in the College of Physicians was marked by a series of controversies. He succeeded, however, in becoming a candidate in 1607, a Fellow in 1609, and a Censor on four occasions. Wright, as amanuensis, must have been kept busy by his eccentric master, who produced a great mass of obscure works. His servitude continued until Fludd's death in 1637.

Simeon Fox's Patronage

Left once more destitute, Wright sought the help of Dr. Simeon Fox, son of the martyrologist, President of the College (1634–40), and noted for his generosity and for his encouragement of young scholars. Through the endeavours of influential men Wright secured his patronage; through his

own qualities he gained a friend. "Henceforth he lacked neither counsel nor help in what could inform his mind, polish his style, or perfect his manners." Fox had been born in the household of the Duke of Norfolk, had throughout his life moved among distinguished men, and was not only a great physician but a travelled and cultured man. In 1602 he had witnessed the ceremony at Padua when Harvey received his diploma.

Fox furnished Wright "with a wealth of choice books, likewise he gave his pupil an allowance for meals, or arranged for them to be prepared for him." He also introduced his apprentice to the study of botany and aroused his interest in anatomy; "and truly Robert was pliant in all these things. In a single summer he mastered the uses, names and forms . . . of trees, fruits and herbs." Wright perfected a method of transplanting seedlings and keeping them alive in his lodging by the use of numberless sheets of wet blotting-paper, "so that even in the dreariness of autumn and the hoariness of winter, all waxed green." Dr. Baldwin Hamey declares that Wright's room looked like a provision market with its baskets of plants.

When Wright turned to anatomy the appearance of his room was less pleasant. He not only dissected there every type of animal but engaged in vivisection. The product of his work, the viscera either untreated or boiled, reminded visitors of the shambles adjoining the College. The human limbs and entrails, which "he impaled on rusty and foul stakes," recalled grim scenes on Tower Hill. Fox paid the expenses involved in obtaining all this material, and the College presented to his pupil the bodies of a lion, recently arrived from Africa, and of a Libyan ostrich. He made comparative studies of these and mounted the skeletons and the ostrich skin for the College museum.

Wright became so skilled in dissection that Fox chose him to carry out this duty when the Lumleian and Gulstonian Lectures were held, thus avoiding the unwelcome attendance of a surgeon within the College.

Fox died in April, 1642, leaving a sufficient sum in trust for the payment of Wright's fees when he should eventually become a candidate and Fellow of the College. According to Wright's own statement he had by then been in practice for four years, and, since such action within the City or its environs for seven miles would have exposed him to the risk of imprisonment and fine by the College, it must be presumed that he was working in the country. Country practice was under no clear supervision at this time, in spite of Henry VIII's joint board of churchmen and physicians and the occasional and legally questionable visitations of the College.

Simeon Fox lay in state at the College and was buried with great pomp and solemnity beside the fine tomb which John Caius had raised to Thomas Linacre at St. Paul's; but the closing notes of the chanted requiem did not mark the end of his influence in College affairs, and to this may be due some of the success of his former apprentice. Fox left him to the care and protection of another of his disciples, Dr. Baldwin Hamey. Himself a medical graduate of Leyden and, by incorporation, of Oxford, Hamey advised Wright to follow the same course. The obtaining of a foreign degree and then an English one by incorporation overcame two obstacles: it solved the problem of learning any medicine at Oxford or Cambridge, and it provided the English degree which was required by the College of its Candidates and Fellows. A licence, and no more, could be obtained on a foreign degree, but it was by no means certain, and might be long withheld or be restricted in some form.

A Brief Academic Course

Hamey arranged for Wright to go immediately to Leyden, "providing him with all things necessary for the journey and with letters of introduction to the various professors in the medical faculty," which he entered on August 30, 1642. He was now 42 years old, and not, as the printed copy of Leyden's *Album Studiosorum* states, 22. The letters were presumably an affidavit of Wright's apprenticeship and practice, which, added to Hamey's and his father's reputation at Leyden, were sufficient to meet the regulations. On September 11, 1642, following his dissertation *De Lue Venerea*, Wright obtained his degree.

Returning to London, Wright was successful in obtaining the College licence. He also applied to Cambridge for a doctorate by incorporation. On February 15, 1643, he added a second degree to his name. Hamey relates that Wright now "gave in his name to the College of London with a view to undergoing examination [as a Candidate] by the Censors, by whom all things having been performed according to custom, the house assembled, I [Hamey] being his surety and sponsor." The statement by so eminent an authority as Hamey that the examinations had followed the customary course is illuminating, for the procedure appears to have consisted only of formalities in his case. On March 6, 1643, the ceremony to which Hamey refers marked their successful conclusion. The usual three years' interval before election to the Fellowship contracted to eight months, and Wright was received into that order on November 11, 1643.

When a Fellow was received it was customary for him to deliver an oration. Two alternative speeches, prepared by Hamey, have survived, one diffident and one confident, the choice depending on the mood of his audience.

Marriage and Success

We hear next that Wright "provided himself handsomely with sufficient good clothes . . . and not long after he aspired to the hand of Anne Boteler in marriage, the daughter and sister of Sir Thomas and Sir William." From now on for the brief remainder of his life his career was one of brilliant success: "his name increased more and more throughout the City, and he was elected by the Surgeons as lecturer in anatomy and by our College as Gulstonian lecturer, and was also intended by them for the office of Harveian Professor of Anatomy. His practice also began to increase; he was handsome, debonair, dignified, elegant, painstaking and skilful, especially in dissection. . . . On the death of his patients, lest he should be criticized, he took sufficient care straightway to open the body and demonstrate to the onlookers the inevitability of death." As his experience of post-mortem appearances increased his reputation grew, and he came to "be called for in consultation by leading physicians." Invariably courteous, he "could report something of value in determining the cause of death, if not in preventing it. Whence it befell that, scarcely three years qualified (which he volunteered to me [Hamey] without conceit), he was earning almost a thousand crowns a year."

On April 3, 1646, the College invited Wright to be Gulstonian Lecturer for 1647, but he did not live to deliver the lectures. Worn out by overwork, much reduced in weight, and suffering from sleepless nights owing to his wife's fatal illness, he was overtaken by septicaemia on September 10, 1646. Six days later, in spite of every available measure adopted by his friends, he died in his home in the parish of St. Edmund the Martyr, Lombard Street.

A shrewd contemporary observer compared Wright to Vesalius and to Harvey, yet, to-day, so utterly has his memory faded that the comparison appears false. But perhaps the falseness lies in the standards by which the eminence of historic medical figures is assessed: the application of the two tests—what books did they write, what discoveries did they record?

After years of struggle with poverty, with no more than twelve days of academic residence, Wright yet managed so to influence his contemporaries during his four years of practice that he established a living tradition. On his death Hamey wrote of him that "by his fine example, by his reputation and his learning, he has encouraged [others] to achieve the highest."

My thanks are due to the Harveian Librarian for permission to quote from the manuscripts in the College library, and to Mr. G. H. Brown for his assistance in elucidating many Latin passages.

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ROYAL SOCIETY RESEARCH FELLOWSHIPS

Dr. C. E. Lumsden has been appointed the second Henry Head Research Fellow of the Royal Society from October 1, to work at the Maida Vale Hospital for Nervous Diseases and the National Hospital for Nervous Diseases on disseminated sclerosis.

Dr. D. R. Wilkie has been appointed the first Locke Research Fellow, from October 1, to work at University College, London, on energy relations in muscular contraction. Frank Spiller Locke, formerly reader in physiology at King's College, London, who died in 1949, left part of his estate to the Royal Society for the endowment of Locke research fellowships in experimental physiology and pharmacology.

The council of the society has also appointed for the first time two Stothert Research Fellows, each for two years in the first instance, from October 1. Mr. J. R. Vane will work at the Nuffield Institute for Medical Research, Oxford, on the mechanism by which histamine produces gastric secretion, and Dr. J. M. Walshe at University College Hospital, London, on amino-acid metabolism in liver disease. The Stothert Research Fellowships were established by the bequest to the Royal Society of the residuary estate of Dr. John Henry Stothert, a lecturer in pharmacology at University College Hospital, who was drowned at the age of 27 in a canoeing accident in Austria in 1937. The bequest came to the society in 1948 after the death of Lady Stothert.

Reports of Societies

CHEMOTHERAPY OF TUBERCULOSIS

From July 10 to 13 a very successful conference was held in Dublin under the auspices of the Medical Research Council of Ireland to discuss the chemotherapy of tuberculosis. The conference was unusual in that it gathered together biochemists, bacteriologists, and clinicians in discussion on the various stages of the search for effective antituberculous agents.

Dr. E. LEDERER, of the Centre National de la Recherche Scientifique, Paris, spoke on the chemistry and biochemistry of the tubercle bacillus. After outlining what is known of its chemical structure, he discussed the findings that virulent strains contain free mycolic acid and a high content of lipopolysaccharides. Very little was yet known of the biochemical processes leading to tubercle formation; the formation of casein might be due to inhibition of proteolysis. Inhibition of leucocyte migration had been ascribed to cord formation and to lipopolysaccharides.

B.283 and B.390

Dr. VINCENT C. BARRY, Director of Laboratories of the Medical Research Council of Ireland, gave a lecture on "An Organic Chemist's Approach to the Chemotherapy of Tuberculosis." He stressed the limitations of the present anti-tuberculous agents; there was still no known drug that would diffuse readily in caseous material. The ideal drug might be reached by the rational approach, by such work on the metabolism of the tubercle bacillus as had been described by Dr. Lederer. Up to the present six drugs had been found effective in the experimental animal: the sulphones, *para*-aminosalicylic acid, the thiosemicarbazones, streptomycin, and two substances synthesized in his laboratories, known as B.283 and B.390. These last substances had been elaborated after work on derivatives of lichens found to resemble chaulmoogra oil. B.283 was active *in vitro* in the presence of serum, and had a suppressive effect on tuberculous disease in guinea-pigs. Results were not quite as good as with streptomycin. It had been tried with success in humans for renal tuberculosis and for leprosy; no definite results had been obtained in pulmonary tuberculosis in man, "possibly because rather hopeless cases were treated."

This paper was followed by an interesting discussion on the empirical and the rational approach in the biochemist's search for effective drugs: a representative of one drug firm confessed that he tested for anti-tuberculous activity every new compound produced by the firm. Dr. G. T. BARNES, of Nigeria, gave an account of his work on the treatment of leprosy with B.283; he considered it more effective than any other drug tested so far. Dr. R. J. W. REES, of the National Institute for Medical Research, made a brief and intriguing reference to a new compound with no activity *in vitro* but considerable activity *in vivo*.

Laboratory Appraisal of Anti-tuberculous Agents

At the third session Dr. W. H. FELDMAN detailed the procedures that must be followed in the preclinical appraisal of anti-tuberculous agents. Though the crucial test was the performance of the drug in the patient, there could be no substitute for preliminary trial in experimental animals. *In vitro* results were often poorly correlated with results *in vivo*. He analysed the relative advantages of tests in the chick embryo, in baby chicks, hamsters, rabbits, mice, and guinea-pigs. He considered guinea-pigs to be the most dependable, but they were more expensive, and demanded more space, more time, and larger quantities of drug. He proceeded to describe what should be the programme of experimental procedures: routine screening tests, short-term crucial tests, and long-term crucial tests. But success in the experimental animal was no guarantee of success in humans. His paper was followed by an interesting discussion, impossible to summarize.

Dr. GEORGE BROWNLEE, speaking on "The Present Status of Antibiotics in Tuberculosis," discussed in general some of the problems encountered in present-day evaluation of drugs. The problem of drug resistance must be considered in relation to any new drug, whatever the mechanism—mutation or adaptation—of the resistance; any effective antibiotic should help to prevent the development of resistance to streptomycin when combined with that drug. One rational approach in the search for new drugs was the study of the role of hypersensitivity in the development of tuberculous lesions. Another lay in the study of the factors causing acquired resistance; it might be possible to find the essential substance of B.C.G. or of heat-treated vaccines which conferred immunity. Dr. D. G. MADIGAN described a series of cases treated with streptomycin, P.A.S., and old tuberculin. Dr. D. A. MITCHISON and Mr. G. W. P. DAWSON made interesting contributions to a discussion on the nature of drug resistance.

Thiosemicarbazones

Dr. GERHARD DOMAGK, speaking at the fifth session on "The Chemotherapy of Tuberculosis with Thiosemicarbazones," gave the history of work on this group of drugs. He stressed that *in vitro* they were more effective than P.A.S. or streptomycin when in the presence of *para*-aminobenzoic acid. In the experimental animal the best results were obtained by a combination of streptomycin and TB I. The dosage required was related to the inhibitory levels found *in vitro*; the upper limit was set by the side-effects. There was a direct relation between size of dose and the curative effect. He believed that the undesirable side-effects were due to excessive destruction of tubercle bacilli, especially where there was much caseous material or cavities; the same effects on the liver could be seen experimentally after injecting dead bacilli. Dr. J. FRANCIS pointed out that, while TB I was experimentally more effective than streptomycin when given at the time of infection, it was less effective in established disease. Dr. A. R. MARTIN described work on TB III, which appeared to be better tolerated in man than TB I and produced blood levels three times higher for equal doses. Dr. M. M. NAGLEY described work with the thiosemicarbazones in a series of 18 patients: he had found TB III less toxic and more effective than TB I.

Clinical Trials

Dr. MARC DANIELS spoke on "The Clinical Evaluation of Potential Chemotherapeutic Agents in Pulmonary Tuberculosis." Considerable progress in this type of work had been made during the past five years; it was now possible, in a relatively short space of time, to evaluate scientifically the clinical effectiveness of a new drug for tuberculosis. Before embarking on a large-scale clinical trial of a drug found effective in the experimental animal, it was useful to have preliminary small clinical investigations to study toxicity in man, and to gauge the effect of the drug in observable superficial tuberculous lesions. If results of these pilot trials were promising, a fully organized clinical trial might be justified. The basic methods of trial in pulmonary tuberculosis were: comparison with clinical course before treatment, comparison with untreated controls, comparison with the effect of a known drug, and study of the effect of combination with streptomycin in preventing streptomycin-resistance. This latter method had become a most valuable one; fewer cases were needed than for a trial measuring clinical effect. Dr. Daniels described the various rigorous procedures and the team-work necessary for the proper conduct of a clinical trial. The Medical Research Council trials in England had been made possible only by the voluntary co-operation of a great many expert clinicians and pathologists.

At the final session Mr. T. J. D. LANE described a small trial of B.283 in genito-urinary tuberculosis. Twelve patients had been treated, nine of whom had had nephrectomy. In eight cases not rendered bacteriologically negative by streptomycin four had become negative on treatment with B.283; two, however, had later relapsed. The dose was 1 to 4 grammes a day. The drug, a dark red powder, made patients the colour of a "technicolour Indian." No trial had yet been made of streptomycin in association with B.283. Another drug, B.53, produced by Dr. Barry, had shown some effect in tuberculous cystitis.

Preparations and Appliances

A MACHINE-MILKER FOR THE BREAST

Dr. R. A. RATCLIFF, paediatrician, Oxford Regional Hospital Board, writes: Existing mechanical means of extracting milk from the lactating breast are described as breast "pumps," and by that description they are also condemned. Modern dairy science emphasizes the distinction between lactogenesis and galactopoiesis, and this differentiation has stimulated the study of the latter process, which is the flowing of the milk as distinguished from its secretion. Normal galactopoiesis is characterized by a rise of pressure within the breast, produced by contraction of the alveoli, causing an active flowing of milk from the nipple. Any means of emptying the breast can be physiological only if it promotes this natural reaction.

To devise a mechanical appliance which will have a baby-like action and cause physiological alveolar contraction, completely and comfortably emptying the breast, has occupied my attention for some years. I believe that the response of the lactating breast is the only permissible test of such an appliance, and I have therefore relied solely on the opinion of my patients in its development, not being content with the design until they all declared the action to be "just like a baby." Seven machines of the kind described here have been successfully operated in differing circumstances during the last eighteen months.

The appliance consists of: (1) A cabinet measuring 15½ by 13 by 8 in. (39 by 33 by 20 cm.) containing a vacuum pump operated by a small electric motor running off the mains or off a 12-volt car battery (Fig. 1). Sterilizing equipment is

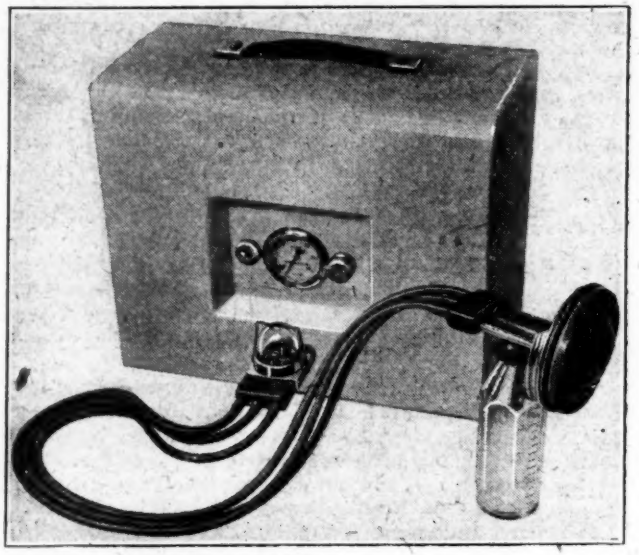


FIG. 1.

provided, and this is stored inside the cabinet. There is also space for storing the other external parts. The pump supplies both a constant and a pulsating partial vacuum. An interceptor to prevent the milk accidentally entering the pump is fitted between the facepiece and the vacuum pump. (2) Three ¼-in. (0.32-cm.) bore rubber tubes carry the vacuum, one constant and two pulsating alternately. (3) The facepiece, which has parts corresponding to the baby's throat, gums, mouth, and face, is built up on a metal base and holds a standard feeding-bottle, so that the constant vacuum reaches the throat and mouth through the bottle (Figs. 2 and 3). On the other side of the metal base is fixed an oval piece of moulded rubber which corresponds to the baby's gums, being moved by the suction operating alternately inside and out. Over all a thin diaphragm of moulded rubber is stretched from the throat behind through the mouth, shaped for the lips, and carried out to the rim, forming the face.

The degree of vacuum is adjustable by the mother, who usually seems to prefer 4 to 5 in. (10 to 12.5 cm.) of mercury. Clear instructions are given that she must not allow the least degree of discomfort.

The constant vacuum sucks milk through the short wide throat into the bottle, and the pulsating vacuum moves the gums and provides: (*a*) the massaging action of the baby's face; (*b*) the biting action of the gums; and (*c*) the regular

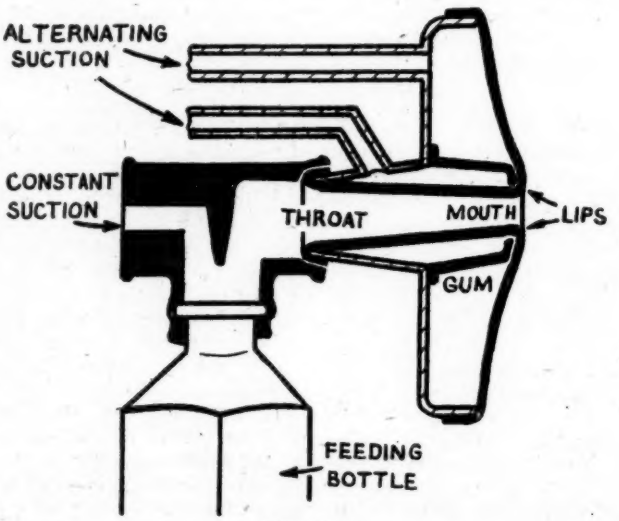


FIG. 2.

squeeze on opposite sides of the nipple produced between the baby's tongue and hard palate. This movement, together with the constant suction along the throat, is exactly that illustrated by F. Charlotte Naish.* Careful attention has been paid to easy thorough cleaning and sterilization by an untrained person, and in this respect the apparatus is designed in accordance with advice obtained from the National Institute for Research in Dairying. The short milk passages have no recesses or corners where milk residues may collect, and all parts in contact with milk are readily replaceable.

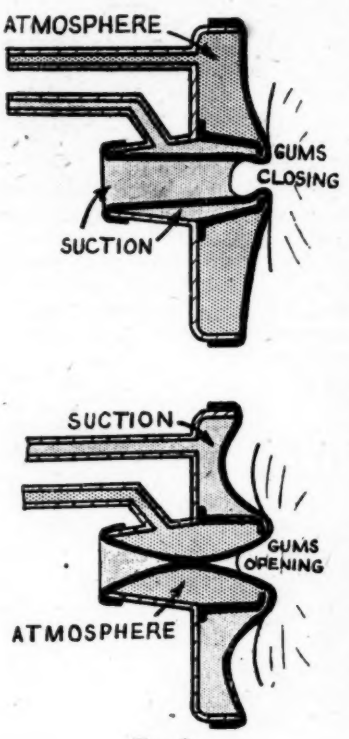


FIG. 3.

In use, feeds are taken from the breast just as if the appliance were a real baby, but one, moreover, possessing the virtues of patience and gentleness. This feeding is a very comfortable process even in early lactation; the breast is completely emptied, and the yield is steadily increased. A premature baby can be left in hospital after the mother has gone home, and by feeding only to the machine at home the supply of milk is steadily increased. This milk is free from any contamination for taking to the hospital, while the physiological "let down" encouraged by the appliance makes the baby's feeding very easy even at the first attempt. Similarly, the appliance will comfortably maintain lactation if a baby requires admission to hospital without his mother or if a baby cannot suckle by reason of cleft-palate or other causes.

Where such abnormalities as delayed lactation, depressed nipples, or mastitis are present the painless action has been found to save the breast-feed in cases in which it would otherwise have been lost.

The machine is made for me by Gascoignes (Reading) Ltd., Reading.

*_Breast Feeding_, p. 26. 1948. Oxford University Press, London.

The world's population has increased by 826,000,000 since the beginning of the present century, nearly half of this total being contributed by Asiatic countries, according to a statistical study made by the World Health Organization. In addition, the study shows that the world population has nearly quadrupled in the last three centuries and that two-thirds of this increase has occurred within the last century alone. Of the 52 countries listed, only one—the Republic of Ireland—has actually shown a decrease (7%) during the first half of this century. The population went down from 3,200,000 to 3,000,000. The largest percentage increase of all was registered in Argentina, where the population rose by 251%. Argentina is followed by Cuba (231%), Colombia (217%), and Brazil (191%). On the whole, the American continent has recorded the greatest relative increase during the past fifty years, whereas the rate of increase has been slower in Europe than anywhere else. The population of Europe rose only 36% (not including the U.S.S.R.) during the half-century under review.

Correspondence

Lung Carcinoma Statistics

SIR,—In answer to a Parliamentary question (June 28) the Minister of Health is reported (July 7, p. 60) to have replied: "Deaths recorded as due to carcinoma of the lung were 2,121 males and 694 females in 1940 and 3,720 males and 807 females in 1949." This answer, it appears to me, will inevitably be misinterpreted and lead to confusion, for the figures given are very different from those published by the Registrar-General of England and Wales. For 1949 they are, in fact, less than half those given by the Registrar-General under the customary heading of "cancer of the lung and pleura."

The explanation of this difference cannot lie in the exclusion by the Minister of the few deaths specifically ascribed to the pleura, and it is impossible to believe that "carcinoma" would be interpreted in such a narrow pathological sense as to exclude deaths described on the certificate as due to "cancer." It must be presumed, therefore, that the Minister has omitted from his totals the large numbers of deaths which are attributed to cancer of the bronchus. This sub-group does not appear separately in the reports of the Registrar-General, for, as in the *International List of Causes of Death*, it has invariably been classed with cancer of the lung. Since, however, these descriptions are used interchangeably in ordinary medical parlance it is clearly necessary to take the two sub-groups together when considering the number of deaths "due to carcinoma of the lung."

The figures required to answer the question by Dr. Barnet Stross are, therefore, those published by the Registrar-General under "cancer of the lung and pleura"—namely, 4,047 males and 1,180 females in 1940 and 9,327 males and 1,945 females in 1949. Not only, it will be seen, are these figures very much greater than those given by the Minister, but they reveal also an appreciably steeper increase over the ten years.—I am, etc.,

London, W.C.1. A. BRADFORD HILL.

⁂ The Minister confirms that he excluded cancer of the bronchus from his totals.—ED., *B.M.J.*

Infective Hepatitis

SIR,—It may be of interest in connexion with Dr. L. E. Glynn's article (May 26, p. 1198) to note the frequent occurrence of bilirubinuria without significant elevation of serum bilirubin in the pre-icteric stage of infective hepatitis. This was described by Budd in 1846 (*Diseases of the Liver*, p. 368, Philadelphia, Lea and Blanchard), but it is unusual for bilirubinuria to be so gross as to be detectable on inspection of the urine. Using the simple tests for bilirubin in urine, this phenomenon has been observed (Pollock, M. R., *Lancet*, 1945, **2**, 626) in as many as 86% of cases, and thus is of some diagnostic value. For this purpose the methylene-blue test has been used successfully (Gellis, S. S., and Stokes, J., jun., *J. Amer. med. Ass.*, 1945, **128**, 782), and it has the merits of simplicity and high sensitivity; but the more complicated Fouchet test has the added advantage of freedom from false positive results.—I am, etc.,

Glasgow. A. G. BAIKIE.

Combined Reductions of the Lower Jaw and Nose

SIR,—In their very lucid article (July 7, p. 26), Mr. P. Clarkson and his colleagues agree that a combination in one operation of bilateral osteotomies of the mandible together with a nasal reduction causes anxiety in the post-operative period. This combination of procedures is liable to cause extreme anxiety and is therefore contraindicated. These two operations can be performed with a suitable time interval, when a good airway can be maintained throughout treatment and the same final result obtained.—I am, etc.,

St. Thomas's Hospital, S.E.1. RICHARD BATTLE.

The "Good Doctor"

SIR,—In your issue of June 30 (p. 1505) there is an extensive account of the conference-course on medical teaching which was held during two days in London recently. A statement was made early that the object of medical education is "to train an undifferentiated good doctor," and most of the discussion could be regarded as taking this as a basis. There is no record that anyone described what a good doctor is, and yet an agreement on that is necessary. I believe that a good doctor exercises a double function: he relieves a patient's anxiety by making the patient believe that he will do all that is possible to remove any physical or mental cause of the anxiety, and then he does whatever is known for that purpose. After all, patients are reasonable, they do not expect a cure every time. Tolstoy in his novel *War and Peace* saw the essential point, and stated that doctors are necessary because of the feeling of the patient and his friends that "something should be done." It is to the honour of the medical profession that it tries so hard to find the best thing to do. Our present doubts are due to thinking so much of the means that we forget the aim. It is not enough to tell students to be less technical in their outlook; we must show them that the aim of mental assistance to the patient must be followed whether our technical means are good or not.—I am, etc.,

London, W.1. J. M. ALSTON.

Intrathecal Use of Chloramphenicol

SIR,—We have read with interest the note in the *Lancet* by Mr. V. M. Coppleson on the local use of chloramphenicol (July 14, p. 65). We have recently had experience of the successful intrathecal use of chloramphenicol in the treatment of two cases of meningitis caused by penicillin and streptomycin-resistant staphylococci. So far as we are aware, this method of administration has not been previously described. A full account of these cases has already been prepared and is in the course of publication.—We are, etc.,

K. F. ANDERSON.
London, S.E.1. F. G. ELLIS.

Antihistaminics and Burns

SIR,—I would suggest to Dr. A. E. Milne and his colleagues (July 14, p. 117) that there is no need to restrict the exhibition of the antihistamines to burns seen in the first four hours.

The first burn I treated was started on "anthisan" two days after the scald (*Lancet*, 1949, **1**, 936). Also a small series of six with "anthisan" and six without was divided up by Dr. J. H. Shelswell at Manchester Royal Infirmary to test my claim that by the fourth day of treatment you can tell the difference. I was only in doubt in one case, and I later found that this patient had taken the tablets only on the first day.

Also against Sevitt's work (*Brit. J. exp. Path.*, 1949, **30**, 540) must be placed the claim in Samson Wright's *Applied Physiology* (p. 563, 1945, London) that after severe burns the concentration of histamine in the blood may rise fourfold in the course of a few days, and this is roughly paralleled by the clinical state. Lastly, oedema of the face in two burnt patients has been observed to subside in 24 hours so that they were able to take nourishment by mouth.

When we compare this with cortisone, which is reported to have no effect on oedema, then I am sure that Dr. A. E. Milne and his colleagues will not feel alone in following John Hunter's dictum of "try the experiment."—I am, etc.,

Manchester. S. SHUBSACHS.

SIR,—It was with interest that I read the letter of Dr. A. E. Milne *et al.* (July 14, p. 117) on the use of antihistamines in the treatment of burns. A trial of the effect of the local application of a cream containing 2% "phenergan" with dibromopropamidine isothionate (0.15%) (May and Baker, Ltd.), and of the effect of the antihistamine when given systemically, is at present being undertaken in this hospital. A number of burns of varying depths and extent have been treated in this way with results which have so far been encouraging. It is hoped to publish findings later when a sufficient series has been collected.—I am, etc.,

Royal Hospital for Sick Children, Glasgow, C.3. D. A. MACPHERSON.

Adrenaline Cream in Rheumatism

SIR,—I have read Dr. E. G. L. Bywaters's letter (July 14, p. 120) in which Dr. Howell's findings are refuted. It is quite clear from the report of the research subcommittee and the methods employed in its investigations that the cream has been used in a haphazard manner. The technique of treatment to be followed in this new therapy and upon which satisfactory results alone can be achieved have been neglected (or not complied with).

The basis of treatment of non-articular rheumatism with adrenaline cream is that by its use the "myalgic spots" are exactly located and can thus be more efficiently treated. In my experience these spots are the source of pain and spasm, and they are often some distance away from the painful area. It is therefore apparent that this research subcommittee has applied the cream only to referred areas of pain and soft tissue spasm, for it is quite impossible to massage these spots deeply for five minutes at the first treatment. The pain caused would be so intense that the patient would be in a state of collapse before a minute had elapsed. Ten seconds or so is sufficient, depending upon the patient's threshold of pain, his age, and the tone of his muscles. I have emphasized in all my papers the necessity of concentrating treatment on these spots, not only for the relief of pain, but for a speedy amelioration of the symptoms of the disease, and this has been adopted by Dr. Howell (Moss, L., *Med. World, Lond.*, 1950, **72**, 486).

The technique of treatment has been described in detail in my later papers on this subject (*Brit. J. Physiother.*, 1949, November, p. 11; ibid., 1949, December, p. 9; *Med. Pr.* 1950, **223**, 515; *Practitioner*, 1951, **166**, 168), which seem to have escaped the attention of the research subcommittee of the Empire Rheumatism Council. I would add that I shall be pleased to demonstrate my technique of treatment to any member of the research subcommittee.—I am, etc.,

London, S.W.1. LOUIS MOSS.

SIR,—While it is not within my province to comment on the clinical evaluation reported by Dr. E. G. L. Bywaters (July 14, p. 120) I must cross swords with him on his price comparisons.

Far from simply assessing the basic cost of the ingredients of a specified formula, to market a product of this kind would involve the following costs, even if this was done by a Government department: (1) Research: Fundamental or developmental or both; (2) Production: Materials, including packaging, labour, expenses and overheads (rent, rates, heat, light, machinery, etc.), analytical control; (3) Distribution: Administration and distributing expenses. Dr. Bywaters's price comparisons are therefore valueless and appear to indicate a bias which one would not have expected from a research worker.—I am, etc.,

W. G. HOLLIS,
Secretary, Proprietary Association of Great Britain.
London, W.C.1.

Diverticulitis of the Transverse Colon

SIR,—As a corollary to Mr. B. Rowlands's interesting account (July 7, p. 29) of a case of localized diverticulitis of the transverse colon, I should like to draw attention to a similar case which was treated here recently.

The patient, a man of middle age, was admitted with a history of generalized abdominal pain, which later settled in the right iliac fossa. A diagnosis of acute appendicitis was made, but at operation a normal appendix was found. A hard tumour was felt in the transverse colon just distal to the hepatic flexure, and on the assumption that this was a carcinoma a right hemicolectomy was done. Examination

FIG. 1.—The excised half-colon showing the large diverticulum distal to the hepatic flexure and a number of smaller ones on the ascending colon. Adherent omentum and pericolic fat have been dissected away.

of the excised bowel showed that the hard tumour was an inflamed diverticulum with omentum matted around it, while, as the photograph of the dissected specimen shows, a number of uninflamed diverticula, not noticed at operation, were present on the caecum and ascending colon. A post-operative barium enema showed yet another large diverticulum in the transverse colon, just distal to the ileo-colic anastomosis.

The lesson to be learned from this case is clear. A hard tumour found in the ascending or transverse colon of a patient who has presented with acute abdominal pain should be carefully examined and dissected free of omental adhesions before it is assumed to be a carcinoma. Uninflamed diverticula in the ascending and transverse colon should also be looked for, as their presence will suggest that it is infection in one of them

FIG. 2.—Post-operative barium enema showing a large diverticulum lying over the vertebral column just distal to the ileo-colic anastomosis.

which has caused the patient's illness. Most inflamed diverticula in the proximal half of the colon can easily be removed, once they have been cleared of adhesions, by cutting across the narrow neck and repairing the small opening left in the bowel with a two-layer suture.—I am, etc.,

Cambridge. R. E. B. TAGART.

Causes of Infertility

SIR,—In your report of July 7 (p. 51) of the papers on cervical hostility read to the conference on fertility at Cambridge the figures given in my paper are omitted, although those of Miss D. H. Shotton and Miss N. Laughton are quoted. This is particularly unfortunate, as there are considerable differences in our findings on bacteriology. I should be grateful if you could publish the following brief summary.

In a series of 190 cases the Sims post-coital test was negative in 150, equalling 79%. Of these there were 100 cases, 66%, in which the semen was subfertile. This means that there was true hostility in the remaining 33% who had normal semen. In a total of 205 cases there were 108 clinically abnormal, equalling 54%. Of these there were 13 cases infected with *Bact. coli*, two with streptococci, and one with staphylococcus (coagulase positive), equalling 15%. There was one case with a pure growth of pleuropneumonia-like organisms. In 30 cases specially examined for virus and inclusion bodies none were found. A control series of 43 women who came for contraception, and who all had had one child, was investigated bacteriologically, but no pathogens were recovered.

The considerable differences between our two sets of figures were discussed at the meeting after the paper, and may perhaps be explained by the following points which then emerged. (1) The smallness of Miss Laughton's series —32 cases as against 205. (2) Her preliminary preparation of the cervix involved the application of spirit before taking swabs, which might well alter the mucus. (3) Her controls were in fact other *sterile* women who had a satisfactory post-coital test. As was pointed out in the discussion, such women could not really be regarded as satisfactory controls, since the real test of a normal control must be the ability to produce a child and not the microscopic appearance of her mucus. It was for this reason that I chose as my controls a series of normal women who had already borne one or more children and who sought contraceptive advice.

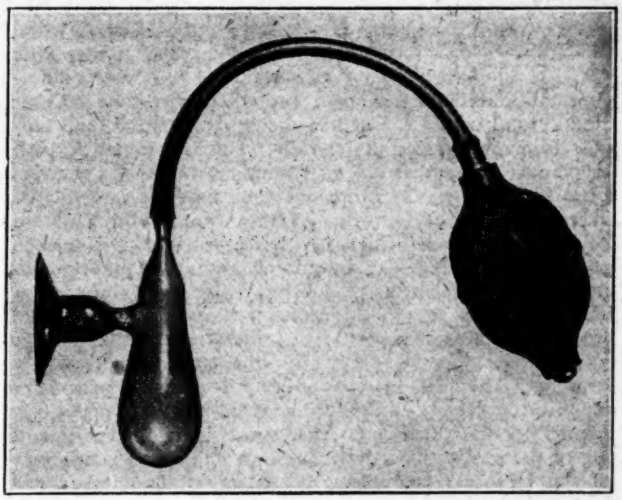
Nevertheless I should like to add that, notwithstanding the points raised above, Miss Shotton made a valuable contribution to the problem of cervical hostility in her differentiation of the two groups which she encountered.—I am, etc.,

Urmston, Lancs. BERNARD SANDLER.

A Breast Reliever for Domiciliary Practice

SIR,—The ordinary manual breast reliever used by patients outside hospitals almost invariably fails to achieve its purpose, mainly because of the brutality of its action and the severe pain it often causes.

My instrument is designed to emulate in its action as nearly as possible the sucking action of an infant. In



practice it has been found to be comparable with the gentle action of the electrical machines used in hospitals. The prototype was improvised from a Victorian glass bulb (which incidentally was operated by the mother sucking the end of an attached tube) and a Higginson's syringe attached so that air was sucked out of the bulb. This was found to produce a gentle, easily controlled action, which the mother could readily use herself, and which effectually relieved a

turgid breast. The instrument consists of a high-quality glass blown to form a large reservoir with an ordinary glass nipple shield fused to it. The air outlet is at the top so that milk is not drawn into the rubber tube and bulb. This bulb has two valves arranged so that a negative pressure is created in the reservoir. In practice the apparatus works best with a fairly rapid series of small contractions, thus simulating normal suckling. It can be used to relieve a turgid breast, or to rest a breast with a cracked nipple; the milk drawn off can be fed to the baby until the crack heals, thereby frequently enabling breast-feeding to be continued. This breast reliever has been well tried out by two district midwives in the last three years, and can be recommended for use in domiciliary practice or small hospitals without electrical equipment.

I am indebted to Mr. Michael Franklin, of Messrs. J. G. Franklin and Sons, for his encouragement and help in producing several instruments, and to the district nurses and mothers who have co-operated in the trials.

—I am, etc.,

Much Hadham, Herts. PETER MCA. ELDER.

"Formalin Arthritis"

SIR,—I have read with great interest the article by Parkes and Wrigley (March 31, p. 670), as I have been working on this arthritis for about a year (Silva Lafrentz, C., *Algunos Aspectos de las Artritis*). At the end of the article the authors say that their "experiments do not confirm the statement by Selye [*British Medical Journal*, 1949, **2**, 1129] that 'self-maintaining chronic inflammatory process' develops in the ankle-joint, showing 'little or no sign of regression for weeks after the last injection.'" For this reason the authors studied the effects of treatment on acute conditions resulting from formalin injection.

I have tried to reproduce the chronic phase of "formalin arthritis" in 85 white rats, under the following different conditions: intact animals, animals nephrectomized unilaterally and with 1% NaCl in the drinking water, and animals adrenalectomized unilaterally. I have injected beneath the plantar aponeurosis 0.1 ml. formalin (Merck) of a strength rising from 1% to 5%, three or four times at intervals of several days. Only in four of the animals did I obtain a typical chronic arthritis with the characteristics described by Selye—"cartilage-like indurating granulomatous vegetation." In two, the arthritis developed (see Fig.) about 40 or 50 days after the last injection of 5% formalin. In the other two male rats, adrenalectomized unilaterally, the chronic arthritis developed ten days after the last injection of 3% formalin. These lesions continued to develop for periods of one to three weeks. In the four animals scabs had previously formed on the feet, but no abscesses. In pilot experiments one of these cases of arthritis was not influenced in any way by the local and parenteral cortisone, while another was made a little worse by parenteral D.C.A.

Consequently I believe that at present chronic arthritis by formalin can be produced, but with difficulty and rarely. For this reason, and until better results can be obtained, I agree with the authors that "formalin arthritis" in rats is unsuitable for use as a screening test for substances proposed for the treatment of rheumatic diseases.—I am, etc.,

Vina del Mar, Chile. CARLOS SILVA LAFRENTZ.

Bronchography by Endotracheal Tube

SIR,—I described (*British Medical Journal*, 1950, **1**, 140) a modification of the Magill endotracheal tube for bronchography in adults. The technique described permitted the introduction of iodized oil selectively into the bronchial tree under direct radiological vision with minimal discomfort and risk to the patient. It has come to my notice that certain misapprehensions exist concerning this technique.

One of these is that it is difficult to maintain inhalational anaesthesia throughout the procedure. I should like to point out that the tubes were never designed for this purpose. Intubation is performed under topical analgesia, and the large outer tube is to allow adequate respiratory exchange while the radio-opaque oil is introduced through the small inner tube. The object in having the smaller tube *inside* the other tube is to make it as smooth as possible for passage through the nose. Blind nasal intubation under topical analgesia is a surprisingly simple manœuvre and much less upsetting to the patient than intubation by the oral route. A second complaint is that the tubes are too long in some cases. They are, however, readily shortened by splitting along each side of the small inner tube, and then across, leaving an appropriate length of inner tube still protruding. Finally, some batches of tubes are rather hard in consistence. These are readily softened by repeated boiling.

I have done over 250 cases by this technique, to the satisfaction of radiologist, patient, and myself, and some radiologists now perform their own intubations without difficulty.—I am, etc.,

Leicester. W. R. SPACEK.

Prune Stone Ileus

SIR,—Foreign bodies in the intestine occasionally lodge in a pathological lesion, and by causing acute symptoms bring to light latent disease.

A man of 80 was admitted to hospital with a short history of increasing constipation, culminating in an attack of acute intestinal obstruction which could not be relieved by turpentine enemata. A laparotomy revealed a ring carcinoma in the lower sigmoid colon, and a temporary caecostomy was carried out. For the succeeding three days, the patient passed several loose faecal stools per rectum and the caecostomy remained surprisingly inactive. As this development was somewhat unexpected, a check barium enema was done which showed an obstruction at a site corresponding to the laparotomy findings.

Three weeks after the first operation the growth was resected and the bowel anastomosed. On opening the specimen of resected gut the proximal lumen was found to be empty save for a prune stone which could be wedged into the narrow channel through the growth, like a bung.

It is presumed that the stone became wedged into the growth in this manner, causing total obstruction, and that it slipped back as soon as the tension was released following the caecostomy, thereby allowing the passage of faeculent fluid through the rectum for the next few days.

The patient made a good recovery and was discharged from hospital after operative closure of his caecostomy. He stated that he had last eaten prunes two weeks before admission.—I am, etc.,

York. J. K. WILLSON-PEPPER.

Rehabilitation of Geriatric Cases

SIR,—The rehabilitation of the aged presents many problems; elderly patients confined to bed for an indefinite period have a tendency to deteriorate both physically and mentally; therefore, whenever practical, we endeavour to make the patient ambulant and self-reliant as soon as possible. In cases of spastic hemiplegia involving the lower limbs we use a specially designed appliance (Fig. 1) to straighten the leg. This consists of two parallel side steels with five sliding attachments. The first is known as the stand; this is adjusted to raise the patient's leg to the required height. There are also adjustable thigh and calf corselets on sliding

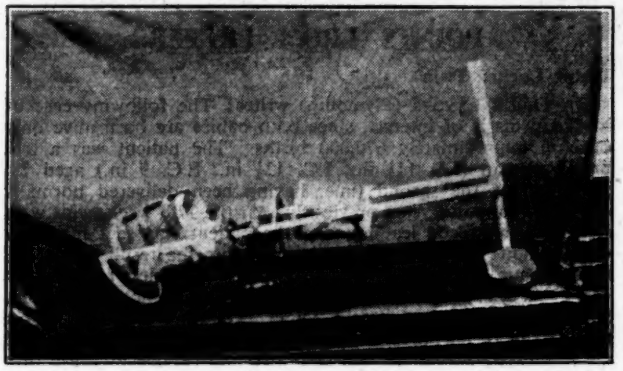


FIG. 1.

lock bars. A shaped knee pad is placed over the knee-joint and attached to the straightening mechanism under the limb. The limbs can be exercised with this instrument by turning a small handle attached to it. A gentle even pressure is applied with little or no discomfort to the patient. A special knee cage with a variable knee lock is used in conjunction with the remedial exercises. This appliance can be adjusted and locked to any degree of flexion suitable to the patient's condition. With this the patient is taught to walk again.

In many cases of this nature the condition is advanced before medical attention is sought and rehabilitation is retarded by the patient's lack of confidence. During the early stages in walking training patients often become nervous, fearing they may fall. To overcome this problem we use three-legged walking-sticks (Fig. 2) made in duralumin. This walking-stick, which is called the "Warral," has non-skid stops attached to each leg. In the oblique leg a stabilizer is inserted to give the appliance balance. This is an important feature. The handles are adjustable and the weight of the stick is approximately 30 oz. This appliance gives the patient a feeling of security, and in view of its extreme lightness walking exercises can be reasonably prolonged without tiring the patient. We are constantly adjusting our methods of treatment with geriatric patients, and our main objectives are (1) to restore as fully as possible loss of function and to enable the patient to regain his confidence and to get about with the minimum dependence upon others, and (2) to help the patient to live intelligently with his residual disability.

FIG. 2.

For the production of the special appliances described herein my great thanks are due to Mr. Leslie Ralph, of Remploy Limited, who has worked with great interest and much patience in very close collaboration with me in designing these aids.—I am, etc.,

Isleworth, Middlesex. MARJORY WARREN.

Prefrontal Leucotomy

SIR,—In the large literature regarding prefrontal leucotomy scant attention has been paid to the moral problems involved; perhaps because it lies in the nature of the current scientific approach to man that such problems are either denied relevance or are believed to belong to a different domain in a dualistic epistemology. The article by Dr. G. D. F. Steele (July 14, p. 84) raises these problems in a disturbing manner, not least because the author fails to make any reference to the fundamental issue involved. Since he makes no attempt to defend his position, the author must assume that his readers will agree that it is a sufficient therapeutic aim to restore a patient to "functional" efficiency and that the loss of the ability to suffer is altogether a result to be welcomed. These assumptions follow the mainstream of modern neurophysiological thought, but in this instance they transcend the theoretical argument and proceed to the practical demonstration that man as a machine can be better than man in the human situation to which, as some believe, suffering belongs by definition.

The author's assurance that the patient has once again taken up her household duties with efficiency does little to relieve one's doubt whether she may still be regarded as a proper person to rear children and whether her presence in sickness and in health will be capable of providing her husband with any comfort beyond that which depends on the cooking of meals and the sweeping of floors. That an anxiety state of eighteen months' duration could be thought sufficient indication to subject a patient to prefrontal leucotomy may at least have the welcome result of shocking medical opinion into reconsidering the whole problem in its basic aspects.

With the widening of psychosomatic concepts to include a growing variety of disorders among disturbances of the personality it may be asked whether the time has not come when spiritual euthanasia must become the subject of legal control.—I am, etc.,

Stirlingshire. JOSEPH SCHORSTEIN.

Dental Anaesthetics

SIR,—I write with some trepidation as a mere dental surgeon in support of Dr. J. G. Bourne (June 9, p. 1330) and his contentions regarding the use of nitrous oxide and oxygen anaesthesia, particularly in the dental surgery. Anyone who has ever seen a wrecked dental unit or witnessed a chairside wrestling match (even when the anaesthetic is administered by a skilled operator) cannot but agree with his postulate (1) qualified by (5). Postulate (2) is equally applicable to the dental surgery as well as casualty. (3) is undeniably true. McKesson, one of the virtuosos of "gas," achieved his astonishing results by skilful and controlled anoxia or "hypoxia," but few people would risk exploiting his technique to-day. (4) requires no comment. (6) is admitted in the annotation "A Whiff of Gas" (p. 1314).

The unsatisfactory nature of gas as administered in the dental chair is aggravated by the necessarily open mouth and airway. This last can be prevented, of course, only by proper packing off of the oesophagus and intubation. I realize that this is impracticable in the chair, but it is necessary if a further danger is to be avoided, that of falling back of the tongue into the airway or blockage of the airway by an exfoliated tooth or fragment. Even worse than temporary blockage, of course, is the inhalation of a septic fragment and its resulting lodgment in a bronchus. The danger of such happening is not very great, even with the usual flimsy gauze pack, but the fact that it can and does occur at all is good enough reason to consider open "gas" as being too dangerous for use in the practice of dental surgery. Further disadvantages are the often fearsome screams emitted by an anaesthetized patient and the fact that operating time is all too short for efficient exodontia. Exodontia under gas is smash-and-grab, and the number of roots and fragments left behind in this form of operation in a year are countless.

There are two alternatives: proper packing off and intubation and the use of a more effective narcotic in a theatre equipped to deal with the emergencies that do occur with general anaesthesia, or, if this is impossible, use of local anaesthesia. This in the hands of the properly trained dental surgeon is adequate for extensive oral surgery in both profundity and physical extent of the areas anaesthetized. There are mandibular and maxillary nerve blocks available which are effective, rapid in effect, simple to administer, and allow of patient co-operation during the course of the operation and which do not require recovery rooms or the staff to attend them.

The dean of the faculty of dentistry in the University of Sydney in which I received my training (Professor A. J.

Arnott) feels so strongly about this matter that the students are not taught the administration of N_2O but are trained very thoroughly in the use of local anaesthesia. He teaches that the use of open anaesthesia for dental or oral surgery is indefensible.—I am, etc.,

London, S.W.2. DONALD J. RITCHIE.

Gallamine Triethiodide and E.C.T.

SIR,—The papers by Drs. O. S. Thompson and A. Norton (April 21, p. 857) and by Drs. R. H. F. Smith and D. L. C. Thomas (April 21, p. 860), together with other recent contributions to the literature, suggest that the use of E.C.T. can be extended to relieve cases that would otherwise go untreated. The question arises now whether all E.C.T. should be modified by a curarizing agent or whether only selected cases should be so treated. My own experience at this hospital may be of help. In the past three years I have treated some 50 cases, the early ones with D-tubocurarine hydrochloride, the later ones with decamethonium iodide (C10), and the most recent cases with gallamine triethiodide. In all cases premedication has been with thiopentone, and atropine 1/75 gr. (0.8 mg.) has been given with the curarizing agent. Over half the cases treated suffered from cardiovascular disease—e.g., hypertension, cardiovascular degeneration, and mitral stenosis. Three of these had had a slight hemiplegia previously, one following an earlier course of E.C.T. Of the remainder, in 10 cases there had been a previous fracture of the dorsal spine and the rest suffered from diverse conditions, including rheumatoid arthritis and recent abdominal operation. The oldest patient treated was aged 81 years. It is worth reporting that hemiplegia is not rare following unmodified E.C.T. and that its results may be more disabling than crush fracture of the dorsal vertebrae.

My experience confirms the main findings of the authors, and I feel that gallamine triethiodide will come to be the drug of choice in this hospital. One must question, however, the practice of using curarizing drugs as a routine. If one takes care that the patient is treated on a hard mattress placed on fracture boards with a firm pillow under the thoracic spine, the number of dorsal crush fractures occurring is very low, although in my opinion it is the commonest complication of unmodified E.C.T. Fortunately all these cases get better, but as there is some risk of litigation they are obviously best avoided. Cases of cardiovascular disease carry more risk to the patient in the shape of cardiac failure or even rupture and cerebral haemorrhage. In this mental hospital many thousands of treatments are given each year, including a large number of treatments to out-patients. It would be impracticable, and in my view unnecessary, to give all these patients a curarizing agent.

I have found that the symptoms and signs of crush fractures of the dorsal vertebrae occur more commonly in out-patients. There is therefore a great need in the average out-patient department for an agent which will produce softening of the fit in young muscular patients but which does not require the time-consuming additions of thiopentone and insufflation with oxygen. In my view neither D-tubocurarine chloride, C10, nor gallamine triethiodide should be used unless an adequate closed-circuit resuscitation apparatus is available. I have used "myanesin" (10 ml. of 10% solution) with fair success for this purpose. It has the additional advantages that it relaxes the patient comfortably before the electrodes are placed in position and that recovery is rapid and complete afterwards. Its chief disadvantage is that it may cause considerable and sometimes painful thrombosis of the veins.

E.C.T. is one of the safest treatments in the field of psychiatry, and it is therefore up to us to keep it safe—and simple, so that we can use it in patients' homes and in less well equipped hospitals. I would therefore continue to advance a plea for careful selection of cases and for curarization to be carried out only in the presence of adequate equipment for administering oxygen to an apnoeic patient.—I am, etc.,

Warlingham Park Hospital, Surrey. R. A. SANDISON.

POINTS FROM LETTERS

Living Locked Twins

Dr. O. Ll. LANDER (Plymouth) writes: The following case of locked twins is of interest, since both babies are born alive only once in approximately 670,000 births. The patient was a tall, broad woman (I.S. 11½ in., I.C. 12½ in., E.C. 9 in.) aged 28, pregnant for the second time, having been delivered normally of a 7-lb. baby five years previously. At the 37th week twins were suspected, a breech leading, and the patient was sent for *x*-ray examination on the following day. Before the result was available labour started at 10 p.m. and membranes ruptured at 12.30 a.m. The midwife arrived at the patient's home at 2 a.m., found toes presenting at the vulva, and sent immediately for medical aid. The breech (L.S.A.) came down very slowly and an episiotomy was done. In spite of good expulsive efforts with strong contractions progress continued to be slow until the baby was born as far as the scapulae. There was no further advance, and pressure on the after-coming head had no effect. The baby was by then attempting to breathe, so an internal examination was made. This revealed that the head of a second foetus was presented below, and preventing the descent of, the head of the first, the chins being impacted. The babies were firmly wedged in the capacious pelvis (R.O.P. and L.S.A.). Trilene and gas-and-air were being self-administered throughout, and during the relaxation of the uterus and the voluntary muscles both heads were pushed above the pelvic brim and separated. This allowed the first baby to descend, and it was then delivered without difficulty at 5 a.m. This baby, a boy of 4 lb., shocked and white, was handed to the sister, who laid it gently on its side in a warm blanket with its head low and cleared the air passages; it responded with no further treatment. Ten minutes later, after spontaneous rupture of a second bag of waters, the other twin, a girl of 5 lb., was delivered by a second nurse. This baby was lusty at birth. . . . In this case the pelvis was exceptionally large and the two babies could enter it together. The slow descent of a small baby from a very large mother might have led to a suspicion of some abnormality, because the contractions and bearing-down were strong.

Adder Bites

Dr. C. A. E. I. BROWNLEE (Stirlingshire) writes: In the summer of 1934 I saw two cases of adder bites. Both were aged about 14. The girl I did not see till a week or 10 days after she had been bitten, but even then she still had a swollen and slightly tender finger. The boy I saw within half an hour of his being bitten. He had obtained a piece of cord which he used as a tourniquet. The fang-marks, on the right little finger, were quite easily seen, so they were opened up, and potassium permanganate crystals rubbed in, after which the patient was taken home and put to bed. . . . Apart from the swelling and oedema, which travelled slowly up the arm as far as the shoulder, and as slowly receded, and the subsequent bruising, the only other noteworthy points were a mild rise of temperature (99° F.—37.2° C.) and slight delirium on one or two nights. Recovery was complete in 8 to 10 days, apart from slight tenderness, which lasted for some little time longer, of the bitten finger.

Flat Feet

Dr. E. MOORHEAD (Winnipeg) writes: My daughter aged 7 had flat feet, and had been under the care of a leading orthopaedic surgeon for a long period. Plates broke, exercises aroused no enthusiasm, and a tendon transplantation was declined. My family spent a year in Hastings in the early part of the first war. On returning from France at the end of 1916, I was delighted to find that the flat feet were cured. As no treatment had been carried on, I could only reason that it was due to running about on the beach barefoot. When the tender feet came in contact with shingle or a sharp bit of shell, there was a sudden tightening of the intrinsic muscles of the feet, with consequent development. When I returned to Canada I suggested to the surgeon that his young patients should play barefoot in his gymnasium, and that dried split peas should be sprinkled on the floor. I have no evidence that a trial of this was made.

Correction

Dr. J. V. GARRETT writes: The second sentence of the second paragraph of my letter "Eosinophils and Blood Clotting" (July 21, p. 176) should read: "De Takats has reported that the eosinopenia after operation . . . if eosinophilia occurs subsequently."

Obituary

LUDVIG HEKTOEN, M.D.

Dr. Ludvig Hektoen, who had an international reputation as a pathologist, died in Chicago on July 5, aged 88.

Ludvig Hektoen was born in Westby, Wisconsin, and he studied medicine at the College of Physicians and Surgeons in Chicago. Graduating in 1887, he quickly made a name for himself as a pathologist, and for the first thirty or so years of this century he was professor and head of the department of pathology at the University of Chicago and also at Rush Medical College. In his early years Hektoen studied at several centres in Europe, and he was a member of a number of Scandinavian learned societies. Much of his work was devoted to cancer research: he was one of the founders of the Chicago Tumor Institute; in 1930 he was made chairman of the Cancer Research Institute of Chicago, and from 1937 to 1944 he was executive director of the National Advisory Cancer Council, United States Public Health Service. In addition he was chairman of the National Research Council from 1936 to 1938, having been for some years previously chairman of the Division of Medical Sciences.

Hektoen was distinguished both as a contributor to many scientific journals and as a leading medical editor. He was editor of the *Journal of Infectious Diseases* from its foundation in 1904 until 1941, of the *Archives of Pathology* from its foundation in 1926, of the *Proceedings of the Institute of Medicine of Chicago*, and of the *Transactions of the Chicago Pathological Society*. Many honours came his way. The American Medical Association awarded him its Distinguished Service Medal in 1942. A year later, at the time of his eightieth birthday, the John McCormick Institute for Infectious Disease, of which Hektoen had been a founder, was re-dedicated in his honour as the Ludvig Hektoen Institute for Medical Research of Cook County—a fitting commemoration of his many notable achievements in pathology, bacteriology, and immunology.

We are greatly indebted to Dr. Howard T. Karsner, of Washington, D.C., for the following appreciation: It is a privilege to say a few words about Ludvig Hektoen, who was not merely an acquaintance but an exceedingly good friend over the course of not less than 30 years. No one who knew Hektoen failed to appreciate his keenly analytical mind and his insistence upon scientific precision in experiment and expression. When he was editor of the *Archives of Pathology* he was most helpful in consideration of papers submitted, in that his comments invariably improved the quality of the presentation. On casual meeting he gave the impression of a certain degree of austerity, and unless his visitor got to know him that impression might persist. Nevertheless, throughout all his associations with assistants and colleagues, both young and old, he was the essence of kindliness. No problem great or small presented to Dr. Hektoen failed to elicit comments that were helpful in its solution. With this inherent trait of kindliness went a gentleness of approach and expression which was unexampled. Throughout these many years I have benefited inestimably by his friendship and help. In addition to close personal relationships, my association with him in the American Association of Pathologists and Bacteriologists and the Division of Medical Sciences of the National Research Council was more than agreeable; it demonstrated continuously his great scientific acumen and his fine analysis of situations. His loyalty to those assistants who worked with him will always be remembered by them and those who knew of his support. American science has lost a great figure, one whose peculiar attainments mean that replacement cannot be contemplated.

W. E. TANNER, F.R.C.S.

J. C. N. writes: I should like to add the tribute of a one-time house-surgeon and latterly a surgical colleague of my old friend William Tanner to what has already been said about him.

Tanner's outlook on surgery was influenced from the start by the powerful personality of Arbuthnot Lane, whose house-surgeon he had been. He always spoke of him with the greatest respect and regarded him as the outstanding surgeon of a brilliant age of surgeons. The pupil differed from the master in at least one pre-eminently important respect, for, unlike Lane and some of his brilliant protégés, Tanner's work was characterized above all by the qualities of his judgment, both on purely professional and also on specifically personal aspects of the case. The first consideration with him, whether he was advising or operating, was always the question of what particular line of action would best suit the particular patient, and it was this characteristic, rather than his personal charm, his energy, or his considerable operative ability, which made him so valuable as a consultant.

His operative technique was characteristic of the Lane school, to which he always remained faithful. He was quick, gentle, and had an absolute horror of doing unnecessary damage; in his prime he was as quick an operator as I have seen when the occasion demanded it. His operative work was always practical to a degree, and he inclined to a conservatism which increased with the experience of years. While he was interested in new ideas and methods and was very well informed, he was too honest to be partial to passing fads and theories which lacked the backing of experience and which offended his uncommon degree of practical common sense. Although the kindest of men, he never hesitated to condemn what he considered to be humbug or self-advertisement. I have heard him say that his house-surgeons were his most severe critics; as one of them I may say that I would have chosen him to advise or operate on my family or myself with every confidence.

His personal life was a happy one, and he was a most popular man. I do not think I have ever come across anybody who did not like him. He was excellent company, full of information about all sorts of people and things, and he had a greater knowledge of contemporary members of the profession than anyone I know. He was an excellent chief to work under, and took infinite trouble to teach his juniors in a practical way and to help them on afterwards, for he was genuinely interested in their welfare and affairs.

Recently, as he realized that the sands of time were running out for him, he was too restless and active to be able to contemplate quitting his work before he had to. He made a great effort to keep going till the end. In the event he was spared the decline of activities that he dreaded. He was operating the day before he died, and he went "in harness," as he would have wished to do. Like many another of his friends, I shall greatly miss his cheery and kindly personality, his practical

wisdom and knowledge of people, and the occasional letters and regular Christmas greetings I have received from him for over 20 years.

SIR WALTER JOHNSON, C.M.G., M.B., F.R.C.S.

E. C. B. writes: By the death of Sir Walter Burford Johnson a great Englishman passes from the African scene. Being endowed with great physical and mental energy, he soon made a name for himself as a first-class surgeon and investigator when he arrived in Northern Nigeria. Not only was he a great surgeon, a great investigator, and a very successful D.M.S., but he was also a very great gentleman and a good sportsman. He well earned the high regard in which his memory will always be held—that of a fine man and a loyal friend.

J. SIM WALLACE, M.D., F.D.S.R.C.S.

Dr. James Sim Wallace, formerly lecturer on dental surgery at the London Hospital and on preventive dentistry at King's College Hospital, died on July 13 at the age of 82.

Wallace was born near Glasgow and educated at the Langside Academy and Glasgow University, where he took the B.Sc. in 1889, the M.B., C.M. in 1890, the M.D. in 1893, the L.D.S. in 1895, and the D.Sc. in 1901. He made a special study of the prevention of dental caries and the growth of the jaws and wrote a large number of papers on these subjects. His theories came to have a wide influence, and much of what he taught has formed the basis for views held to-day. He was awarded the John Tomes Prize for work on the prevention of dental caries and the Cartwright Medal and Prize by the Royal College of Surgeons in 1920 and 1925. He was also awarded the Neech Prize by the Society of Medical Officers of Health. He was made an honorary Fellow of the Society of Medical Officers of Health, an honorary member of the British Dental Association, and a Fellow of the American College of Dentistry. In 1948 the Royal College of Surgeons elected him a Fellow in Dental Surgery.

A colleague, J. J., writes: In 1923, when the dental school at King's College Hospital was founded, J. Sim Wallace was on the original staff. About that time he published two important books—one for the education of the general public, stressing the value of functional mastication and the cleansing effect of fibrous foods, the other being academic, on the subject of variations in the form of the jaws. In those early days lectures were held in the clinical room, where there was a dental chair placed in front of three or more tiers of stools on which the students sat. For some reason best known to himself Wallace invariably arrived half an hour before his lecture was due to begin and was usually found by the students fast asleep in the dental chair. When, however, the hour for his lecture arrived, Wallace came to life, and in a quiet and most casual manner gave the students his views on preventive dentistry. He was never dogmatic and would listen to any views put before him with the greatest courtesy. But then he might quietly put in some remark which completely negatived the previous statement. His views on caries are well known. He considered dental caries to be a disease of civilization caused by refined carbohydrates, and in this respect upheld the views of Miller. To other views that were put forward Wallace always had his reply, "I am not a research man. The only research I have done is in an armchair with a wet towel round my head." He did not ignore the research work done by others—far from it: he read it all and gave credit when he thought it was deserved—but he was impatient of the hasty views put into print without what he termed careful and honest thought. On retiring from King's he was not often seen at the hospital, but he always retained an affection and interest in the dental school.

Dr. WALTER EDWARD JOHNSTONE died at his home in Brora, Sutherland, on June 18 at the age of 80. Until his retirement in 1948 he had served the Parish of Clyne faithfully for the long period of 41 years. Johnstone graduated M.B., C.M. at the University of Edinburgh in 1894, having taken his M.A. degree in 1889. Throughout his long professional life he retained an intense pride in his Alma Mater and loyalty to the memory of the great teachers of his day. His knowledge of the classics and of English literature was exceptional, as was his memory, and a ready and apt quotation was forthcoming on all occasions. It was difficult to find any subject on which he was not an authority. He was a delightful companion, ever young in spirit and full of enthusiasm for his work and his manifold other interests. Eighteen years ago he underwent a serious abdominal operation from which he was hardly expected to recover. Although his health was never robust since and he suffered considerably at times, his indomitable spirit carried him through years of strenuous and devoted service to the public. The loss of his wife some years ago was a grievous blow from which he never recovered. Johnstone was a splendid type of family doctor, most scrupulous in all his doings, respected and loved by his patients and his colleagues. In early days he covered his wide district by cycle or on horseback, and in later years his Morris car of ancient vintage was a familiar and welcome sight. He was a master of first-aid treatment in accidents, and his bandaging (now a lost art) was a delight to see. For some years he acted as honorary anaesthetist to the Lawson Memorial Hospital, Golspie. A night call found him always ready and cheerful, for he could never leave his beloved books and go to bed until the early hours of the morning. He had been an active member of the B.M.A. since 1903, and in 1928–9 he was chairman of the Caithness and Sutherland Division. As Chairman of the Sutherland Insurance Committee he did sterling work for many years. One of the older and different type of practitioners has passed on—a man of intellect and ability—and with a great kindliness and irrepressible humour all his own. We extend our sincere sympathy to his three sons and two daughters. —B. S. S.

Medico-Legal

DAMAGES FOR SHOCK

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

In an action brought by Mr. John Foster, K.C., M.P., against the London Transport Executive as a result of a collision between his car and a bus in Piccadilly, Mr. Justice Jones awarded Mr. Foster £750 damages for shock. Liability had been admitted by the Executive.

Mr. Foster's case was that although he had not suffered any physical injury he had received a severe emotional shock, as a result of which he had been unable to drive his car for any long distance since. He was able to drive himself between the Temple and the House of Commons, but for longer journeys had to employ a chauffeur, and he was now highly nervous when in charge of a car and felt that he could not cope with traffic and was a danger to other people.

Mr. Justice Jones said that it was an unusual case, but that he was satisfied by the medical evidence that Mr. Foster had suffered a substantial nervous shock, and that his ability to drive himself had been reduced as a result.

Medical Notes in Parliament

Healthy Upholstery

During the debate on the Rag Flock and Other Filling Materials Bill, which had already passed the House of Lords and was read a second time without a division on July 13, Mr. G. S. LINDGREN said it was true there had been no direct proof that the users of upholstery had contracted disease from it, but infection might so arise, and Parliament should prevent it.

Industrial Dermatitis

Dr. BARNET STROSS asked on July 16 whether the Minister of National Insurance would consider the appointment of a medical officer with experience in dermatology in every industrial centre of any considerable size. Dr. EDITH SUMMERSKILL replied that she did not think this suggestion was practicable.

Aged Sick

Mr. D. KIRKWOOD, on July 17, asserted that distress and bewilderment were caused to relatives of old people who had to be declared lunatics before they could be given beds in hospitals. He advocated legislation to make old age a special class of incapacity and to provide the necessary accommodation in special hospitals for this purpose. Miss MARGARET HERBISON agreed that there was frequent difficulty in arranging institutional care for old people who could not be suitably looked after at home, but she saw no ground for thinking that this could be remedied by fresh legislation.

Toxic Chemicals in Agriculture

Mr. G. H. R. NUGENT, on July 19, asked whether the Minister of Agriculture had considered the opinion of the working party on toxic chemicals in agriculture that, despite the risk to human life, the use of these weed-killers and insecticides should continue.

Mr. TOM WILLIAMS said he thought that the working party's analysis of this problem was sound. In consultation with his department, the organizations concerned had recommended to their members measures for this season on the lines proposed by the working party, and their recommendation that certain proposals should be reinforced by legislation was under consideration.

Domiciliary Analgesia

Mr. PETER THORNEYCROFT, on July 19, asked in which local health authority areas in England and Wales it was proposed to start trials for the use of the new "trilene" machine by domiciliary midwives. Mr. H. MARQUAND replied that the areas had not been determined; they would be selected by a joint subcommittee representing the Medical Research Council and the Royal College of Obstetricians and Gynaecologists, under whose control the trials were to be carried out. The Ministry had not yet received an adequate supply prototype machines.

Mr. THORNEYCROFT also asked whether approval could be given for the addition of the Chassar Moir attachment to all gas-and-air machines in use by domiciliary midwives in England and Wales. Mr. MARQUAND answered that the Central Midwives Board had not yet approved this attachment for use by midwives on their own responsibility. They would consider the matter as soon as the results of a further experiment in its use were available.

Miss MARGARET HERBISON gave similar answers to questions about analgesic services in Scotland.

Mental Disease in Scotland.—2,652 people certified as insane were admitted to mental hospitals under the Lunacy (Scotland) Acts, 1857 and 1862, during 1950. Of these 906 were over 60 years of age.

Army Doctors.—The number of doctors in the Army in April, 1946, was 6,520. In April, 1950, there were 1,532.

Scottish Dentists.—There are altogether about 1,450 dentists practising in Scotland. It is thought that at least another 100 are needed for the school dental service and the local authorities' maternity and child-welfare services.

Road Accidents.—In 1950, 166,592 road accidents involved death or personal injury. Driving under the influence of drink or drugs was the primary factor in 565 cases.

Universities and Colleges

UNIVERSITY OF GLASGOW

The following diplomas were awarded on July 17:

D.P.H.—Grace F. M. Braid, A. S. Caldwell, J. Caldwell, J. H. C. Clarke, W. J. Connelly, Marion H. C. Cornock, T. B. Ferguson, Anne C. V. Greig, J. Hamilton, J. S. McLintock, Alexandrina McPheat, W. R. Plews, W. O. Thomson.

UNIVERSITY OF LONDON

The following candidates at the London School of Hygiene and Tropical Medicine have been approved at the examination indicated:

ACADEMIC POSTGRADUATE DIPLOMA IN BACTERIOLOGY: R. I. Ananthanarayan, A. R. Blowers, I. S. M. Fernando, K. A. Huybers, C. H. Jellard, C. Kaplan, A. M. Khan, Jean V. Knox, J. D. Manning, H. A. Mazloum, C. C. Spicer, M. L. Sur.

The following candidates at the London School of Hygiene and Tropical Medicine have been approved at the examination indicated:

ACADEMIC POSTGRADUATE DIPLOMA IN PUBLIC HEALTH.—Lily G. Arumugam, K. M. Basu, J. P. Brazil, [1]Carol W. Buck, D. H. D. Burbridge, C. G. Burgess, T. W. Carrick, M. J. Colbourne, A. H. R. Coombes, J. D. Cottrell, [1]D. E. Cullington, G. M. Curtois, R. G. Davies, L. E. A. Dearberg, M. Doraisingham, A. G. Farr, M. A. Fawkes, L. V. R. Fernando, Jessie S. Freeman, P. S. Fuller, A. Girby, [1]Margaret I. Hendrie, P. R. Henson, F. R. T. Hollins, I. J. Jeffery, W. H. Jeffrey, E. F. E. Kellar, E. H. Lamb, H. L. Larsen, [1]N. Leitch, I. M. Macgregor, D. H. Mackay, S. Mandal, A. H. Memon, G. A. Mott, See Yook Ng, G. A. R. Perera, R. Perumal, H. B. L. Russell, D. Scott, E. S. Sidey, L. Silverstone, G. A. Steele, O. W. Tenfjord, T. Visuvalingam, A. S. Wallace.

[1]Awarded a mark of distinction.

The following candidates have been approved at the examinations indicated:

ACADEMIC POSTGRADUATE DIPLOMA IN MEDICAL RADIOLOGY.—*Diagnosis:* F. A. Adcock, J. S. Coller, B. Green, Schura Holesh, J. D. Irving, S. A. Kimmel, W. P. Liston, K. G. Paddle, G. F. Swann, D. E. Truscott, C. K. J. Vautier. *Therapy:* R. M. Cunningham, E. D. Jones, P. J. Pablot, Jean K. Ritchie.

Dr. H. E. Sigerist, Professor of History of Medicine in Johns Hopkins University from 1932 to 1947, has been appointed Heath Clark Lecturer for 1952.

The following have been appointed, or nominated for appointment or reappointment, as representatives of the University on the governing bodies indicated in parentheses: Dr. F. C. Wilkinson (Eastman Dental Hospital); Dr. A. E. Clark-Kennedy (Queen Mary College); Dr. C. H. Lack (Royal National Orthopaedic Hospital); Mr. A. G. Cross (St. Mary's Hospital).

Professor A. St. G. Huggett, Professor G. Stead, and Professor F. R. Winton have been appointed representatives of the Board of Preclinical Studies on the Board of the Faculty of Medicine and Professor Esther M. Killick a similar representative on the Board of Advanced Medical Studies, all for the remainder of the current year.

The Mary Scharlieb Research Studentship has been awarded to Dr. Andrew Bogdan, the award to be tenable for one session (1951–2) in the first instance. The Sir William Dunn Scholarship has been awarded to Thomas Hargreaves (King's College).

In the paragraph beginning "Internal students who apply for entry to courses in medicine in and after October, 1953" (*Journal*, April 7, p. 766) paragraph (*b*) has now been amended by the addition of "or, in the case of candidates who have obtained certificate(s) in school or other examinations prior to 1951, by passing at not less than minimum University entrance level in chemistry and physics at the examination recognized by the University for the purposes of their matriculation."

UNIVERSITY OF BIRMINGHAM

In Congregation on June 30 the following degrees were conferred:

M.D.—J. M. French (with honours), J. Tregillus.

PH.D.—*Official:* J. R. Gibson, M.B., Ch.B., D.P.H. *Under ordinary regulations:* Izabelle J. Wajda (*in absentia*).

M.B., CH.B.—[1]Elizabeth H. Buchanan (with second-class honours), [1]R. P. Dyson (with second-class honours), A. J. Allen, Enid J. Barnett, P. V. Best, D. B. Beveridge, E. R. Blay, Madge M. Breward, Margaret E. Burns, Margaret H. Butler, B. C. Calverley, H. J. E. Cox, C. C. Ecob, Katherine M. Eddowes, Margaret G. Fairman, Katharine M. Fussell, F. N. Garratt, [3]S. Ginsberg, Eleanor A. Griffiths, M. G. Hadjiminas, Maureen E. Hardeman, H. Hartill, [2]F. E. Higgins, J. D. Hotchin, R. Hully, J. Ll. Jenkins, G. A. H. Jones, P. L. Kalra, S. G. Lamb, Sheila M. Lane, B. J. Lawley, R. D. M. Lewis, W. H. J. Llewellyn, A. Ll. Lloyd, J. M. London, F. J. Lowe, A. L. McBean, [1]B. G. Moon, M. O. Moore, G. E. Morley, Jean Mottram, Margaret E. Nunn, [1]D. C. Pattison, A. J. Pearce, [3]M. D. Readett, R. S. Rihan, C. Robertson, A. L. Ross, P. H. Round, Hilary M. Rowson, R. G. Russell, Pamela E. Sarjeant, J. W. Tanner, [4]Mavis Wakefield, [2 3]Jean M. Webb, [4]H. C. White, Margaret T. Wood.

The following scholarships, prizes, etc., were awarded in the Faculty of Medicine: *Research Scholarships.—Renewals:* Rachel Franklin (Medical Statistics); Z. Hybs, G. W. Mainwood, and Frances E. Williams (Physiology); A. P. Mead and A. P. Walker (Pharmacology). *Queen's Scholarships.*—Final year, Elizabeth H. Buchanan and R. P. Dyson; Fifth year, P. A. Bramley and Christine C. Wade (divided); Third year, K. J. Hadley. *Ingleby Scholarships,* Elizabeth H. Buchanan (obstetrics and gynaecology), Jean M. Webb (paediatrics and child health). *Special Undergraduate Scholarships,* R. W. Heslop and Gabriel Horn. *Bertram Windle Prize in Anatomy,* P. G. Bevan. *Arthur Foxwell Memorial Medal,* F. E. Higgins and Jean M. Webb. *Sampson Gamgee Memorial Medal,* H. C. White. *Alan Brown Prize in Paediatrics,* M. D. Readett. *Joseph Sankey Prize* and *Priestley Smith Prize in Ophthalmology,* Mavis Wakefield. *Douglas Marsh Ear, Nose, and Throat Prize,* Maureen E. Hardeman. *Russell Memorial Prize,* F. E. Higgins. *Leith-Newman Prize in Pathology,* H. A. Ellis. *John Barritt Melson Memorial Medal,* K. J. Hadley. *Peter Thompson Prize in Anatomy,* V. A. W. Blunt. *John Humphreys Prize,* R. Bradley. *Lawrence Carlton Prize,* C. L. Brady. *Senior Medical Prize,* Jean M. Webb. *Senior Surgical Prize,* Elizabeth H. Buchanan. *Obstetrics and Gynaecology Prize,* Katharine M. Fussell. *Paediatrics and Child Health Prize,* F. E. Higgins and Jean M. Webb. *Junior Medical Prize,* P. A. Bramley. *Junior Surgical Prize,* L. Henry and G. H. Jeavons.

[1]Distinction in obstetrics and gynaecology. [2]Distinction in medicine. [3]Distinction in paediatrics and child health. [4]Distinction in surgery.

UNIVERSITY OF SHEFFIELD

Dr. R. Wheeler Haines has been appointed full-time Senior Lecturer in Anatomy and Dr. D. M. Matthews full-time Assistant Lecturer in Physiology.

NATIONAL UNIVERSITY OF IRELAND

On July 12 the honorary degree of LL.D was conferred on Dr. James M. Carlisle, medical director, and Mr. J. J. Kerrigan, president of Merck and Co. Inc.

ROYAL COLLEGE OF PHYSICIANS OF IRELAND

On July 6 M. J. O'Donnell was admitted, *in absentia,* to the Fellowship of the College and S. M. H. Jaffari was admitted, *in absentia,* to the Membership.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College, held on July 12, Sir Cecil Wakeley was re-elected President for the ensuing year.

Mr. P. H. Mitchiner and Sir James Paterson Ross were elected Vice-Presidents, and Mr. Mitchiner, Sir James Paterson Ross, and Sir Reginald Watson Watson-Jones were readmitted as Members of the Council.

Mr. V. Zachary Cope was appointed Charles Tomes Lecturer for the ensuing year and Mr. William Gissane the first Joseph Henry Lecturer.

Professors and Lecturers for the ensuing year were appointed as follows:

Hunterian Professors.—Sir Lancelot Barrington-Ward, one lecture on swellings of the neck in childhood; Mr. C. E. Dukes, one lecture on familial intestinal polyposis; Professor V. W. Dix, one lecture on ureteric calculus; Dr. S. P. Meadows, one lecture on carotid-cavernous aneurysms and pulsating exophthalmos; Mr. H. H. Stewart, one lecture on partial nephrectomy in the treatment of renal calculi; Mr. S. M. Cohen, one lecture on peripheral aneurysms and arteriovenous fistula; Mr. A. H. Hunt, one lecture on the surgical treatment of Banti's syndrome; Professor F. E. Stock, one lecture on the surgical treatment of cirrhosis of the liver; Mr. John Borrie, one lecture on carcinoma of lung: a clinico-pathological study on 200 resections; Mr. M. F. A. Woodruff, one lecture on the transplantation of homologous tissue and its surgical applications; Mr. Tobias Levitt, one lecture on the status of lymphadenoid goitre, Hashimoto's and Reidel's disease; Mr. G. R. Fisk, one lecture on hyperplasia and metaplasia in synovial membrane.

Arris and Gale Lecturers.—Mr. A. Ruscoe Clarke, one lecture on the prevention of shock and anaemia in trauma; Professor G. McC. Wyburn, one lecture on congenital defects of the anterior abdominal wall; Dr. J. N. Hunt, one lecture on studies of human gastric function.

Erasmus Wilson Demonstrators.—Dr. L. W. Proger, two demonstrations; Mr. A. T. Andreasen, two demonstrations on (1) aortic arch abnormalities and (2) restricted pulmonic flow; Mr. Herbert Spencer, one demonstration on bronchial cancer; Mr. E. W. Grahame, one demonstration on argentaffinomata of the alimentary canal.

Arnott Demonstrators.—Mr. P. H. Mitchiner, two demonstrations; Mr. R. J. Last, four demonstrations.

Professor E. D. Churchill, of Boston, U.S.A., was elected a Hunterian Professor.

Dr. Dorothy McNair was elected to the Fellowship of the Faculty of Anaesthetists.

Dr. S. Engel was appointed honorary research associate of the College in recognition of his research work on the development of the lung.

The twentieth Macloghlin Scholarship was awarded to F. J. C. Millard (Eastbourne College).

A Diploma of Fellowship of the College was granted to W. J. Trezise (New Zealand).

Diplomas were granted, jointly with the Royal College of Physicians of London, to the following successful candidates:

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—D. J. Arkle, E. D. Barlow, A. J. E. Duddington, J. Lomas, J. Pullicino, G. E. B. Scott, G. C. Turle.

DIPLOMA IN LARYNGOLOGY AND OTOLOGY.—A. E. Amoils, J. M. Berry, D. J. Brain, A. N. Cammock, R. G. Chaytor, F. O. Esiri, R. T. S. Goodchild, J. F. Neil, S. Panikkar, A. Rutana, A. K. Sinha, W. A. Sultana, E. Zwiefach.

DIPLOMA IN MEDICAL RADIODIAGNOSIS.—E. Barnett, A. Berrett, Sheila M. Cameron, J. H. E. Carmichael, O. J. Connor, T. M. Corcoran, A. G. M. Davies, Caryl St. J. Davies, E. G. Donovan, D. A. N. Drury, E. T. Feldsted, B. Green, M. Gurudas, C. F. Hutton, A. Kurowski, J. Lawson, G. A. S. Lloyd, A. G. McCarey, S. Matus, Emma L. Stein, D. E. Truscott, C. K. J. Vautier, M. W. P. Ward, D. G. C. Whyte, J. Wilson.

DIPLOMA IN MEDICAL RADIOTHERAPY.—P. E. Côté, Constance M. Davis, Gertrude Goldscheider, J. A. Orr, J. J. Q. Peiris, N. A. Sharples, F. G. Stuart.

DIPLOMA IN ANAESTHETICS.—Lilian Alexander, P. G. Azzopardi, Ann Bardeen, J. B. F. Boyle, Margaret E. Browne, N. G. P. Butler, Nancy S. G. Butt, J. A. Clarke, Lillias J. Dunn, Jean Dutton, H. B. F. Fairley, J. A. Ferris, C. A. Foster, Barbara W. Gerrard, J. B. Gibson, R. A. Green, R. G. R. Grieve, E. Hacker, E. R. S. Hooper, N. G. Johnston, A. K. Karfoot, J. M. Lewis, M. G. L. Lucas, D. J. Lyall, Avril E. M. Matthews, J. E. Norman, Mary Patten, J. P. Payne, D. E. Rowlands, C. Sanger, O. H. Simms, W. Sniper, J. Stovner, W. J. Watt, H. J. Weldon, Edith M. Wilkinson.

DIPLOMA IN OPHTHALMIC MEDICINE AND SURGERY.—R. L. Cahill.

DIPLOMA IN PATHOLOGY.—J. G. U. O. Alexander, M. K. Alexander, J. T. A. Lloyd, J. S. McKinnell.

The following hospitals were recognized under paragraph 23 of the Fellowship regulations: St. John's Hospital, Chelmsford (house-surgeon, for six months); Epsom District Hospital (surgical registrar and two house officers (surgical), all for six months); King George Hospital, Ilford (resident surgical officer and assistant surgical officer, for twelve months, and three house-surgeons, for six months); Middlesbrough General Hospital (house-surgeon, for six months); North Ormesby Hospital, Middlesbrough (two surgical registrars, for twelve months, and two house-surgeons, for six months); Stockton and Thornaby Hospital (surgical registrar, for twelve months, and senior house-surgeon, for six months); Canadian Red Cross Memorial Hospital, Taplow (second house-surgeon, for six months (until July 31, 1953)); Kent County Ophthalmic and Aural Hospital, Maidstone (two senior ophthalmic house-surgeons, senior aural house-surgeon, and junior aural house-surgeon).

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles for the week ending July 7 (No. 27).

Figures of notified *cases* are for: (*a*) England and Wales (London included). (*b*) London (administrative county). (*c*) Scotland. (*d*) Northern Ireland. (*e*) Eire. Figures of *births and deaths* and of *deaths* recorded under each disease are for: (*a*) The 126 great towns in England and Wales (London included). (*b*) London (administrative county). (*c*) The 16 principal towns in Scotland. (*d*) The 10 principal towns in Northern Ireland. (*e*) The 13 principal towns in Eire. A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, Northern Ireland, and Eire, the Ministry of Health and Local Government of Northern Ireland, and the Department of Health of Eire.

Disease	1951 Week Ending July 7					1950 Corresponding Week					1942–50 England & Wales Corresponding Week		
	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	Highest	Median	Lowest
Diphtheria	22	3	11	—	—	63	3	9	1	3	762	290	63
Deaths	—	—	—	—	—	1	—	—	—	—			
Dysentery	368	79	84	6		278	12	87	—	—	278	93	56
Deaths		1		—					—				
Encephalitis, acute	8	—	—	—		6	—	—	—		9	3	—
Deaths		—			—		—			—			
Erysipelas			19	—	2			17	4	2			
Food-poisoning*	109	17		3		187	14		—				
Infective enteritis or diarrhoea under 2 years				15	33					23			
Deaths	11		2	—	1	13		2	—	4			
Measles*	8,544	226	203	230	155	8,955	649	394	165	219	10,269	5,571	2,571
Deaths		—	—	1	1		1	—	—	—			
Meningococcal infection	39	4	17	3		34	2	19	2	2	84	45	24
Deaths		—	1				1						
Ophthalmia neonatorum	40	4	6	—		45	3	10	—	—	106	61	29
Pneumonia, influenzal	358	8	2	4	5	281	13	2	3	—	635	353	281
Deaths (from influenza)†	2	—	—	—	—	1	—	—	—	2			
Pneumonia, primary			139					115					
Deaths	111	16		1	1	107	16		4	3			
Poliomyelitis, acute:													
Paralytic	40	—	16	2	1	212	22	42	10	3	212	16	5
Non-paralytic	60	4											
Deaths§	2	—			—	14	1			1			
Puerperal fever			4				—	10					
Puerperal pyrexia‖	73	5	6	1	1	73	4	1	2	—	182	125	73
Scarlet fever	816	82	130	17	49	1,031	47	118	70	67	1,968	1,302	946
Deaths		—	—	—	—			—	—	—			
Smallpox	—	—	—	—		—	—	—	—				
Deaths				—					—				
(1) Tuberculosis, respiratory			134	37				173	33				
(2) Tuberculosis, non-respiratory			22	10				22	5				
(1) Deaths	110	13	21	6	6	161	20	24	6	11			
(2) Deaths		2	5	2	3		6	9	—	4			
Typhoid fever	7	—	1	1	2	2	—	—	—	5			
Deaths¶	—	—	—	—		—	—	—	—		41	17	11
Paratyphoid fever	23	5	—	1		15	2	—	—	—			
Whooping-cough	3,358	205	276	59	74	3,934	233	281	44	85	3,934	2,240	1,050
Deaths	4	—	—	—	—	4	—	—	—	—			
Deaths (0–1 year)	179	29	26	12	16	191	33	25	9	10	334	293	191
Deaths (excluding stillbirths)	4,210	690	491	101	162	3,934	593	527	102	141	4,717	3,910	3,574
Annual death rate (per 1,000 persons living)			10·1					10·6					
Live births	7,200	1,249	927	230	533	7,131	1,177	950	206	409	9,423	7,579	6,144
Annual rate per 1,000 persons living			19·0					19·1					
Stillbirths	153	18	22			203	27	20			243	203	172
Rate per 1,000 total births (including stillborn)			23					21					

* Measles not notifiable in Scotland and returns are approximate. † Includes primary form for England and Wales, London, and N. Ireland. § The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, and London (administrative county), are combined. ‖ Includes puerperal fever for England and Wales and for Eire. ¶ Deaths from paratyphoid fever are combined with those from typhoid fever.

Vital Statistics

Poliomyelitis

Poliomyelitis notifications in the week ended July 14 (28th week of the year) were as follows: paralytic 50 (40); non-paralytic 70 (60); total 120 (100).

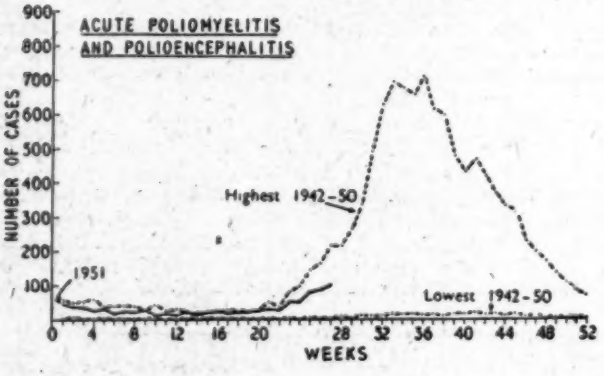
This is an increase of 20 compared with the previous week, for which the figures are in parentheses.

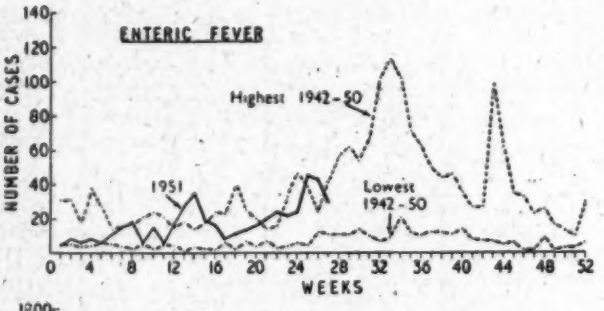
Road Accidents

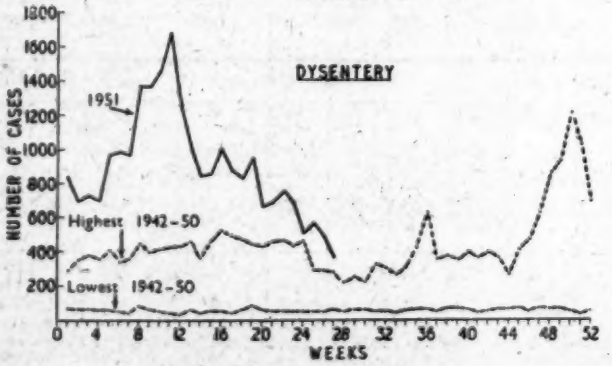
Road casualties in Great Britain during May totalled 18,433, compared with 16,615 in the corresponding month of last year. Deaths numbered 444, an increase of 25, and seriously injured 4,391, an increase of 277. Total casualties in May, 1939, were 20,572. The hour of the day in which total casualties were heaviest was between 5 and 6 p.m., but more persons were killed and seriously injured between 10 and 11 p.m.

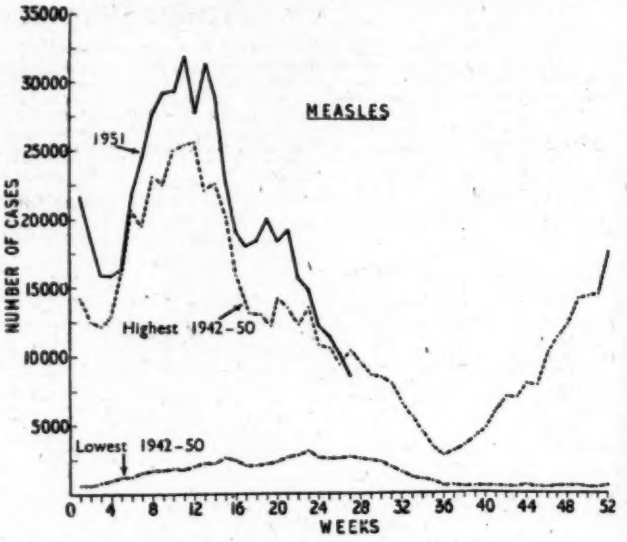
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1942–50 are shown thus -------, the figures for 1951 thus ————. Except for the curves showing notifications in 1951, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

Infectious diseases were less prevalent in England and Wales during the week ended July 7, and falls were recorded in the number of notifications of measles 1,516, whooping-cough 175, dysentery 122, and scarlet fever 88.

The largest falls in the number of notifications of measles were Buckinghamshire 158, Essex 152, and Kent 137, while the largest exceptions to the general decline in incidence were rises in Durham 118 and Yorkshire West Riding 73. The largest fluctuations in the returns of whooping-cough were decreases in Kent 59, Middlesex 51, and Lancashire 48; and a rise of 24 in Glamorganshire was the largest increase. The notifications of scarlet fever were the smallest number for 41 weeks; an increase of 21 in Middlesex and a decrease of 25 in Lancashire were the chief variations in the local trends. The number of notifications of diphtheria was 10 fewer than in the preceding week, and the total was the smallest ever recorded, being 7 below the previous record low level. Of the 22 cases of diphtheria 7 were notified in Lancashire (Liverpool C.B. 5) and 5 in Durham.

The number of notifications of acute poliomyelitis were 13 more than in the previous week. A fall of 9 was recorded in Yorkshire West Riding and of 6 in Warwickshire, the two largest centres of infection in the preceding week. The largest returns during the week were Warwickshire 16 (Coventry C.B. 13, Birmingham C.B. 3); Lancashire 11 (Liverpool C.B. 5); Yorkshire West Riding 8 (Sheffield C.B. 3); Leicestershire 6 (Hinckley U.D. 4); Middlesex 5.

The number of not fications of dysentery was the smallest for 35 weeks. The largest returns were London 79; Middlesex 66 (Edmonton M.B. 35); Lancashire 46; Yorkshire West Riding 29.

Week Ending July 14

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 802, whooping-cough 3,277, diphtheria 25, measles 7,662, acute pneumonia 348, acute poliomyelitis 120, dysentery 292, paratyphoid fever 29, typhoid fever 4.

A request has gone out to chemists from the council of the Pharmaceutical Society that they should give no indication, either direct or indirect, that they sell contraceptives. While the Society considers that they may quite properly sell them, an increasing tendency to draw attention to the fact is regarded as damaging to the reputation of pharmacy, and the Society proposes to take action against flagrant breaches of its recommendation.

Medical News

B.M.A.'s New Telephone Number is EUSton 4499

On Monday, July 23, the telephone number of the British Medical Association and the *British Medical Journal* was changed to Euston 4499 (16 lines).

Physical Medicine Exhibition

The International Congress of Physical Medicine will be held in London in July, 1952, and there will be a small exhibition of apparatus, appliances, and literature produced in Britain. This will be designed to illustrate recent advances in physical medicine. Further information may be obtained from the Honorary Secretary, British Association of Physical Medicine, 45, Lincoln's Inn Fields, London, W.C.2.

The "National Formulary"

The Joint Formulary Committee of the B.M.A. and Pharmaceutical Society met on July 10 under the chairmanship of Professor E. J. Wayne, of Sheffield. For many months they have been engaged in revising the *National Formulary, 1949*, and the preparation of the new edition is nearing completion. An important innovation is the introduction of English titles for the various sections. This may well prove to be the first stage in a change to the use of English instead of Latin in prescribing as in the United States. It will facilitate reference; for instance, it will be possible to group nasal douches and sprays under one heading instead of separately under "Collunaria" and "Nebulae," and mouth-washes will no longer be under "Collutoria." For many reasons it has not been possible to use English titles for the formulae themselves. The English names for the prescriptions will, however, be included with the Latin titles. Another useful addition will be a section containing a pharmacological classification of the preparations in the *Formulary*. This will make for easy reference and should be of great assistance to prescribers. A special subcommittee has examined the prescriptions in the Children's Section to make them more palatable. The taste of many drugs, however, cannot be disguised—for instance, it is difficult to make potassium iodide or male fern palatable. Unfortunately there are no uniform standards for many fruit flavourings, but syrup of raspberry is an exception, and clinical trials have shown that this flavouring agent is liked by most children. It is certainly more effective than syrup of orange and chloroform water, and it is well known that young children do not take kindly to peppermint.

Invalid Children

The Invalid Children's Aid Association has under its own management four special boarding schools for delicate pupils and four recuperative holiday homes; it is also in touch with 40 other such homes, in some of which the association has the use of all the accommodation. In London the association acts as an agent of the L.C.C. for placing invalid children in voluntary homes and schools, the cost of maintenance being borne by the council. To use available funds as widely as possible the council wants to concentrate on short holidays of a fortnight, but it has recognized the need for longer holidays, and allows and pays for maintenance for four weeks if the divisional medical officer confirms the need. More case work, housing reports, and other social work is now being done by local authorities themselves, but the association still accepts cases referred from local authorities and by almoners and obtains a picture of the family life and social surroundings of the invalid and handicapped child. One way of helping families with such a child is to find money for special diets. A study is being made of the needs of chronic sick children, and a special home is to be opened for them. The association would like to hear of any child in the London area who is so severely physically handicapped as to be unable to attend school (not mentally deficient children), and there is an information service to make known the available facilities for helping invalid children at 4, Palace Gate, London, W.8.

Alvarenga Prize Award

On July 14 the College of Physicians of Philadelphia awarded the Alvarenga Prize for 1951 to George W. Thorn, Hersey Professor of the Theory and Practice of Physic, Harvard University Medical School, for his outstanding contributions to our knowledge of the role of the adrenal cortex in health and disease. The Alvarenga Prize was established by the will of Pedro Francisco DaCosta Alvarenga, of Lisbon, Portugal, an Associate Fellow of the College of Physicians of Philadelphia, to be awarded annually by the College of Physicians on the anniversary of the death of the testator, July 14, 1883.

Ortho Award for Study of Sterility

Dr. Albert Sharman, gynaecologist at the Royal Samaritan Hospital for Women, Glasgow, was awarded the Ortho Award of $1,000 by the American Society for the Study of Sterility. This was awarded for his presentation entitled "Ovulation after Pregnancy."

Medical Publisher Honoured

On April 27, 1951, the Harvey Cushing Society presented a plaque to Charles C. Thomas, of Springfield, Illinois, in recognition of his great contributions to medical publishing, especially in the field of neurological surgery.

"British Journal of Tuberculosis"

The latest issue of this journal, now in its 45th year of existence (XLV, No. 3, July, 1951), is a special Festival number which contains a review of the evolution of chest surgery in the past thirty years by T. Holmes Sellors, and a survey of the control of pulmonary tuberculosis in England by Sir Arthur MacNalty, as well as papers on siderosis, renal tuberculosis, the home treatment of primary tuberculosis in children, and other special topics. It is a pleasantly produced, readable, and useful quarterly which at 5s. 6d. an issue is remarkably inexpensive. The editor reports an intention to broaden the *Journal's* scope by inviting Dominion representatives to serve on the editorial board.

University of Natal Non-European Medical School

The new medical school for non-Europeans was opened on February 16 at Durban. The primary object of the school is to train fully qualified medical practitioners for work amongst their own people in their own areas, where the need is very great; in the native territories there is only one doctor to every 22,000 inhabitants. Durban has been chosen as the centre for this training, because there is already a large non-European section covering a wide range of university work and also because it is close to thickly populated native reserves—there are nearly 3,000,000 natives living within a radius of 200 miles from Durban. Social medicine will be a special feature of the training as well as tropical medicine.

Pathologists at Dinner

A large gathering of men and women from many countries assembled at Grosvenor House on July 20 at the banquet of the International Congress of Clinical Pathology, presided over by Sir Lionel Whitby, president of the congress. In proposing the toast of the International Society of Clinical Pathology, Dr. W. Russell Brain, President of the Royal College of Physicians, said that such a congress expressed among doctors a feeling of unity in a divided world. He thought there might be a good case for the establishment of a society of political pathologists, suggesting in a light vein that history might be written in terms of histamine. Specialism, he said, presented problems of integration, and he saw in clinical pathology itself an integrating force as shown when the clinical pathologist met the clinician at the

bedside. In response, Dr. Sidney Dyke said that in 1923 the American Society of Clinical Pathologists was founded, in 1926 the British society. The French Society of Clinical Biology had come into existence during the war, when France was occupied by the Nazis, and in 1947 the French had inaugurated the first international congress. Another event in their history had been the establishment of the European Society of Clinical Pathology, now merged in the International Society.

The health of the guests was proposed by Dr. D. Jaumain, of Brussels, who soon belied his plea that he was not an orator. He had, he said, acted as accoucheur at the birth of the Belgian Society, and in this connexion paid a tribute to his friend Professor E. J. Bigwood. Clinical biology (as the French describe clinical pathology) had, he said, been his mistress for 30 years. When he had been asked to speak it was, he admitted, the first time in his life he had obeyed an order. Perhaps a Belgian had been chosen for this honour because the English remembered that Wellington had once spent some time in Brussels. After paying tribute to one of the inspirers of clinical pathology, Louis Pasteur, he then hailed Sir Henry Dale, whom he described thus: "C'est un type, et c'est un chic type!" He also welcomed the presence of Dr. A. W. Sichel, President of the B.M.A., and gave a charming word of thanks to the ladies, and finally to the lady "La Biologie Clinique." Responding for the guests, Sir Henry Dale said he was really there in the place of Lord Addison, who would have been present but for illness, and to whom he paid a tribute as a member of the first Medical Research Committee and the first Minister of Health. Sir Henry thought he preferred the designation "clinical biology" to "clinical pathology." He pleaded earnestly for a growth of the international spirit in medicine and in all science. With anecdote and reminiscence Sir Henry entertained the company with charm and wit. The health of the chairman, Sir Lionel Whitby, was proposed by Dr. F. W. Sunderman, President of the American Society of Clinical Pathologists. The presence of representatives from so many countries was a source of inspiration and he hoped that this meeting would be a stimulus to the foundation of international societies in different parts of the world. In America they had a close feeling for Sir Lionel, who had recently been a visiting professor at Harvard, and whose daughter had married an American. This toast was seconded by Professor Kourilsky, who praised Sir Lionel's service as a soldier in the first world war, and recalled, too, that he had organized a transfusion service for the Free French Forces during the second world war. At a late hour in the evening Sir Lionel responded briefly, saying that one of the charms of such a conference for him was to see the bibliography come to life.

Publications Received

Twelfth Annual Report, 1950, Tuberculosis Association of India.

Directory of Tuberculosis Institutions in India, 1950, Tuberculosis Association of India.

Prospectus of Courses of Training, 1951–2, The Tavistock Clinic.

Report, 1950, National Institute for Research in Dairying, University of Reading.

Annual Report, 1950, Medical Research Council of Ireland.

COMING EVENTS

Refresher Course on Tuberculosis

The Scottish Branch of N.A.P.T. is holding a refresher course for doctors, nurses, health visitors, midwives, and administrative officials in the University New Buildings, Teviot Place, Edinburgh, 8, for four days, September 18–21. The registration fee is £1 1s. All correspondence and applications should be sent to the Scottish Secretary, Miss A. J. Weir, N.A.P.T., 65, Castle Street, Edinburgh, 2.

Reunion Dinner

A reunion dinner of the 22nd General Hospital will be held at the Stork Hotel, Liverpool, on Saturday, September 29. Further information and tickets may be obtained from Mr. C. Cooke, 17, Greenhill Avenue, Liverpool, 18, or from Mr. A. McKie Reid, F.R.C.S., 86, Rodney Street, Liverpool, 1.

Middlesex Hospital Medical School

The annual dinner of the Middlesex Hospital Medical School will be held at the Savoy Hotel (Victoria Embankment entrance), London, on Friday, September 28, at 7 for 7.30 p.m.

Congress of National Societies of Gastro-enterology

The third European congress will be held at Bologna from April 20 to 26, 1952, under the presidency of Professor Antonio Gasbarrini. The topics of the congress will be acute and chronic pancreatitis and chronic constipation. Requests for registration should be sent to the office of the Secretary-General, Institute of Clinical Medicine (Policlinico S. Orsola), Bologna, Italy, not later than January 30, 1952.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Tuesday

EDINBURGH POSTGRADUATE BOARD FOR MEDICINE.—At Edinburgh University (Anatomy Lecture Theatre), July 31, 4.30 p.m., *"The Anatomy of Cutaneous Sensibility,"* by Dr. A. G. M. Weddell.

WEST END HOSPITAL FOR NERVOUS DISEASES, 40, Marylebone Lane, London, W.—July 31, 2.30 p.m., *"Cerebrospinal Fluid Examination,"* clinical demonstration in neurology by Dr. Woodhouse Price.

APPOINTMENTS

EWING, JOHN A., M.B., Ch.B., D.P.M., Physician, State Hospital at Butner, Butner, North Carolina, U.S.A.

HOBBIN, G. M., B.Com., M.B., Ch.B., D.P.H., Medical Officer of Health for Eton Urban and Eton Rural Districts, and Divisional School Medical Officer.

ST. THOMAS' HOSPITAL, London, S.E.—*Part-time Physician to Cardiac Department*, R. Daley, M.D., M.R.C.P. *Part-time Physician to Departmen of Thoracic Medicine*, D. S. Cadman, M.B., M.R.C.P.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Baster.—On May 9, 1951, at Edmonton, Alberta, to Audrey, wife of Norman Baster, M.D., a daughter—Victoria Vivian.

Feilden.—On June 26, 1951, at Luanshya, Northern Rhodesia, to Dr. Elspeth M. Feilden (formerly Brown), wife of F. A. Feilden, a daughter.

Kyndt.—On July 13, 1951, at the Elizabeth Garrett Anderson Nursing Home, Hampstead, to Mary Elizabeth (formerly Van Hee), wife of Charles Kyndt, M.R.C.S., a second son—Christopher.

Merry.—On July 12, 1951, at Poltimore Nursing Home, Exeter, to Margaret (formerly Field), wife of James Cameron Merry, M.B., Ch.B., a daughter.

Petit.—On July 18, 1951, at Salisbury, Southern Rhodesia, to Dr. Joan Lamplugh, wife of Mr. J. Petit, a daughter.

Rollason.—On July 13, 1951, at Hull, to Margaret (formerly Rowbotham), wife of W. N. Rollason, M.B., Ch.B., D.A., a daughter.

MARRIAGES

Wilkinson—Fairlie.—On July 19, 1951, at St. Cuthbert's Church, Blyth, Northumberland, Frederick James Wilkinson, M.B., B.S., to Mary Cynthia Fairlie.

DEATHS

Bowden.—On July 20, 1951, at Trevose, Riverside Road, West Moors, Wimborne, Dorset, Ellis Campbell Bowden, M.C., F.R.C.S.

Hollings.—On July 16, 1951, at a Scarborough nursing-home, Harold Thomas Hollings, L.R.C.P.&S.Ed., L.R.F.P.S., of 1, Granville Square, Scarborough, aged 82.

Lee.—On July 22, 1951, at 26, Stafford Terrace, Kensington, London, W., Robert Hammersley Lee, M.D.

Price.—On July 17, 1951, at The Hollies, Horton, Gower, Glam, Hôel Parry Price, V.R.D., M.R.C.S., L.R.C.P., D.A., Surgeon Captain, R.N.V.R., retired.

Shanly.—On July 13, 1951, at European Hospital, Nairobi, Hubert Michael George Shanly, M.B., B.S.

Spicer.—On July 16, 1951, at Barton-on-Sea, Hants, Arthur Herbert Spicer, M.C., M.B., B.S., D.P.H., of Graffham, Petworth, Sussex, aged 79.

Steel.—On July 21, 1951, at 61, Church Lane, Wool, Wareham, Dorset, Richard Francis Steel, M.B., B.Ch., F.R.C.S.Ed., Lieutenant-Colonel I.M.S., retired, aged 73.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Fluorine in the Water Supply and Dental Caries

Q.—*(1) Is there any conclusive evidence that dental caries in man is related to a deficient intake of fluoride? (2) Does the addition of fluoride to water supplies prevent caries? If so, in what concentration should it be added? (3) Are any toxic effects or other disadvantages to be anticipated from adding fluoride to a public water supply?*

A.—(1) Little information is available on the incidence of dental caries in the older age groups of communities supplied with drinking water which contains an appreciable quantity of fluorine. There is, however, conclusive evidence that children and young persons belonging to communities supplied with water containing little or no fluorine have, other things being equal, more dental caries on the average than communities supplied with water which contains an appreciable quantity of fluorine. On the other hand, individuals who have spent all their lives in an area with a high-fluorine-content water supply may have a high incidence of caries, while individuals who have spent all their lives in an area with a fluorine-free water supply may be caries-free. It is clear, therefore, that fluorine is only one of the factors influencing susceptibility to dental caries.

(2) Judging by reports coming from those localities in America where fluoride is being added to domestic water supplies, it seems highly probable that fluoride added to water has just the same caries-inhibiting effect as is produced by the same concentration of fluorine occurring naturally in a water supply. Whether the caries-inhibiting effect can properly be described as a prevention rather than a postponement of the onset of caries is not yet settled. As a high fluorine concentration can affect adversely the appearance of the dental enamel, the optimum concentration of fluorine in drinking water may be put at approximately 1 part per million.

(3) If the concentration of fluorine in drinking water slightly exceeds 1 part per million, some slight mottling of the enamel will be observed in a small proportion of the population of the area. Mottling of this extent and degree is of little importance, but when the concentration exceeds 1.5 parts per million of fluorine the incidence of mottling and unsightly pigmentation of the enamel is so high as to rule out the deliberate fluorination of water to that level. There are, however, good reasons for believing that concentrations of up to 5 to 6 parts per million of fluorine—and possibly more—could be tolerated in drinking water without producing any toxic effects or disadvantages other than this damage to the appearance of the dental enamel.

Ion-exchange Resins and Cardiac Failure

Q.—(1) *What are ion-exchange resins? What are their uses and how do they act? (2) Are ion-exchange resins of value in treating the oedema of cardiac failure?*

A.—(1) Ion-exchange resins are granular solids insoluble in water, acids, alkalis, or organic solvents, and containing acidic or basic groups in their surfaces. Those containing basic groups are used for anion exchange, and those containing acidic groups for cation exchange. The modern resins are usually synthetic polymers.

In order to use the resins, a column of the material is uniformly packed in a suitable tube or container and the solution to be treated passed through the column. A cation-exchange resin can, for example, be used in either of two cycles, the acid cycle or the sodium cycle. In the first instance, by the passage of a solution containing, say, calcium ions through the column the calcium ions combine with the resin and are removed from the solution, being replaced by an equivalent amount of hydrogen ion. If, however, the resin is first saturated with sodium ion by the passage of a sodium chloride solution through the column, the excess sodium chloride then being washed out, the resin is converted to the sodium cycle. Passage of a calcium-ion-containing solution through the latter type of column then results in the removal of the calcium from the solution in exchange for an equivalent amount of sodium. Anionic-exchange resins are similarly capable of removing chloride and sulphate ions, etc., from a solution by an exchange with hydroxyl ion.

These materials are used extensively in the chemical industry for the removal of inorganic ions from organic and pharmaceutical preparations, in the recovery of valuable metals, and for water softening. They have also found recent application as anticoagulants, stabilizing whole blood, passed through a suitable sterile column, by removing calcium. Another use is in the separation of the different types of amino-acids derived from the hydrolysis of proteins.

(2) In 1946 Dock first suggested the use of cation-exchange resins by mouth for the treatment of congestive heart failure. Numerous reports have appeared since that time confirming his original suggestion. In 1949 Irwin carried out extensive electrolyte-balance studies on patients with congestive heart failure, and showed that the effect of these cation-exchange resins was to immobilize sodium in the intestine so that it was not absorbed into the blood stream. Their only untoward effect is a tendency to produce a metabolic acidosis as indicated by a reduction in the carbon-dioxide-combining power of the plasma.

The greatest use of the cation-exchange resins appears to be in those patients who are occasionally resistant to mercurial diuretic therapy or who find the restrictions of a low-sodium diet unpalatable. Although these resins will not entirely replace orthodox treatment of congestive heart failure, their use does allow a diet containing at least 3 to 5 g. of sodium a day, together with the less frequent administration of mercurial diuretics. By their use alone it is possible to maintain patients oedema-free over a long period of time, but to do so requires large doses of resin, which may cause minor gastro-intestinal symptoms and a repugnance towards such massive oral therapy. Their correct place appears to be as an adjunct to established methods of treatment, thus permitting a more palatable and attractive diet.

The possibility of two complications should be kept in mind during therapy with these agents. First, low serum-potassium values have been reported during their use in some cases, which may enhance the toxicity of digitalis if this drug is being used in large quantities. Secondly, the cation-exchange resins should not be given to those patients with advanced renal disease, as the damaged kidney is unable to synthesize ammonium ions to cover the acid radicals normally excreted in the urine. One case of severe acidosis has been reported under these conditions.

Gold Pin Pessaries

Q.—*I have recently been asked by a patient about the advisability of her being fitted with a gold pin as a permanent contraceptive measure. Is this a good method?*

A.—The stem and cervical cap of the gold pin or wishbone pessary are hollow, so the instrument is not a contraceptive but an abortifacient. The intrauterine portion acts as an irritant which usually, but not always, prevents or disturbs the implantation of a fertilized ovum. The presence of the metal stem causes chronic cervicitis of varying degree, but of more importance is the fact that the intrauterine wings damage the endometrium. This may be followed by infection, which can lead to widespread pelvic infection, a risk which is increased if a pregnancy is a few weeks old before its development is disturbed. These

complications have occurred so often as to lead authoritative opinion to condemn the use of the gold pin. It is also alleged that the chronic irritation may also lead to carcinoma of the uterus, but this is hypothetical.

Primary Bovine Infections and Resistance to Subsequent Tuberculosis

Q.—*Does infection in man with the bovine type of tubercle bacillus give any protection against the human type of tubercle bacillus?*

A.—The degree of immunity afforded by infection with the tubercle bacillus does not seem to be great, but there is no reason to believe that a healed primary lesion resulting from infection with the bovine type leaves any less immunity than that resulting from infection with the human type.

Cervical Disks and Manipulation

Q.—*A woman of 52 has neuritic symptoms in both arms due to a prolapsed cervical disk. Is manipulation of the spine of value in treatment, and if so what are the indications?*

A.—The diagnosis is almost certainly wrong and probably based on radiographic appearances. When a cervical protrusion passes postero-laterally to press on a nerve-root it produces unilateral pain. When a cervical disk protrudes centrally and backwards, it impinges on the spinal cord. In such a case, manipulation is strongly contraindicated. It is suggested that this patient should be examined for the thoracic-outlet syndrome.

Toxic Reactions to Pethidine

Q.—*What toxic reactions to pethidine are known? I have a patient taking up to 150 mg. daily who complains that his locomotion on a quiet stroll of a quarter of a mile is "queer." I shall be glad to know of any disadvantages in the use of this drug. What alternatives are recommended?*

A.—Not many toxic reactions to pethidine are known, but mental confusion in a mild form is one of them. It is not produced in all those who take pethidine but only in some, just as the mental confusion produced by antihistamine drugs affects only a small percentage of those people who take them.

A person who is taking 150 mg. pethidine daily cannot be expected to be absolutely normal when walking about. All drugs with a powerful analgesic action are bound to give rise to disturbances of the kind described in a proportion of patients. Probably pethidine is the safest of all.

Substances like phenacetin and aspirin are probably ineffective for conditions for which pethidine is required. However, if phenacetin or aspirin will do, they should certainly be preferred. The only other drugs to consider would be morphine or "amidone," and they are more likely to cause disturbances than pethidine. In exceptional people, however, the reverse may be true.

Herbal Tobacco

Q.—*Does a mixture consisting of 50% coltsfoot leaf, 30% clover flowers, 10% rose leaves, 10% lavender flowers, smoked as cigarettes, contain ingredients likely to be harmful to an elderly man?*

A.—It is doubtful whether anyone could affirm that the mixture in question yields nothing harmful, but then there seems no reason whatever why it should do so. The plants named suggest an especially pleasant-smelling garden bonfire. The mixture should contain only extremely minute traces of arsenic, as these plants are not likely to have been sprayed with arsenical insecticides. In this respect they will differ from some North American tobaccos (see Daff, M. E., Doll, W. R. S., and Kennaway, E. L., *Brit. J. Cancer*, in the press), but we do not know that the amounts of arsenic in these are harmful.

Mongolism on Both Sides

Q.—*What are the chances that a woman with a mongol sister who marries a man also with a mongol sister may produce a mongol offspring? There are no other mongols known on either side for two generations back, although on the girl's side there is a mentally deficient nephew.*

A.—A certain degree of familial concentration probably does occur in mongolism, but it is very small. The risk in this instance should be slight. If the girl is, say, 25, the chances are probably considerably better than for the average woman of 40.

Aetiology of Chalazion

Q.—*What is known of the aetiology of chalazion? I have been twice subject to it, and each followed a higher consumption of meat than I had been used to, after a period of several weeks. How can the condition be prevented?*

A.—The common aetiology of chalazion (Meibomian granuloma) is a low-grade staphylococcal infection which gains entrance to a Meibomian duct; the duct becomes blocked and the infected secretion of the gland is retained behind the site of obstruction. Multiple recurrent Meibomian granulomata are often associated with vitamin-B deficiency.

Prevention consists in adequate vitamin-B intake and the application of penicillin eye ointment, 25,000 units to the gramme, to the lid margins at night-time. Staphylococcal toxoid is of therapeutic value in some cases.

Sensitivity to Local Penicillin

Q.—*(a) Does sensitivity to the local application of penicillin (cream, ointment, or lozenge) necessarily imply sensitivity to parenteral administration? (b) What precautions should be taken when administering penicillin parenterally to a patient sensitive to local application?*

A.—*(a)* Yes.

(b) No precautions will prevent the development of reactions such as fever and urticaria, although some relief from them may be obtained by the use of antihistamine drugs. It is better to substitute other treatment. With sulphonamides and other antibiotics to choose from, there are very few conditions which will not respond satisfactorily to one of them.

Boiled Milk or Pasteurized?

Q.—*What advantage has pasteurization of milk over simple boiling?*

A.—Pasteurization has little effect on either the state of emulsification of the milk or its taste; the nutritive value is unaffected.

Boiling makes milk less sweet, and causes other pronounced changes in taste. There is a tendency for the protein to form a skin and for the fat to separate. Prolonged boiling would cause significant destruction of the less stable members of the vitamin-B complex.

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